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PATHOGENESIS OF BUNDLE BRANCH BLOCK

REVIEW OF THE LITERATURE; REPORT OF SIXTEEN CASES WITH NECROPSY AND OF SIX CASES WITH DETAILED HISTOLOGIC STUDY OF THE CONDUCTION SYSTEM

WALLACE M. YATER, M.D.

WASHINGTON, D. C.

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INTRODUCTION

The original concept of the electrocardiographic manifestations of bundle branch interruption, as developed by Eppinger and Rothberger [1] (1910) and confirmed by Rothberger and Winterberg [2] (1913), Lewis [3]

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From the Georgetown University School of Medicine and the Army Medical Museum.

1. Eppinger, H., and Rothberger, C. J.: Ueber die Folgen der Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, Ztschr. f. klin. Med. **70**:1, 1910.

2. Rothberger, C. J., and Winterberg, H.: Zur Diagnose der einseitigen Blockierung der Reizleitung in den Tawaraschen Schenkeln, Zentralbl. f. Herzkrankh. **5**:206, 1913.

3. Lewis, T.: Spread of the Excitatory Process in the Vertebrate Heart, I-V, Phil. Tr. Roy. Soc., London **207**:221, 1916.

(1916), Wilson and Hermann [4] (1921) and others, has been attacked in the past few years to the extent that the term right bundle branch block has been changed to left bundle branch block and vice versa. The main mass of evidence in favor of the original concept was accumulated as the result of experiments on animals, mainly dogs, in which interruption of part or all of one or the other bundle branch, usually by surgical section, was produced in a normal heart. The diagnosis of bundle branch block was then applied to conditions studied in the clinic in which the electrocardiograms resembled those made experimentally.

RESULTS OF PHYSIOLOGIC EXPERIMENTS ON BUNDLE BRANCH BLOCK

When a bundle branch is cut artificially there results an increased amplitude of the ventricular deflections, a preponderance of the ventricle containing the nonmutilated bundle branch, an increased spread of 0.03 to 0.04 second in the QRS complex, with notching of that complex, and opposition in direction of the T wave to that of the main ventricular complex. There is a difference, however, between the electrocardiographic picture produced by section of a bundle branch in the dog and the electrocardiographic picture assumed by analogy to represent pathologic interruption of the bundle branch in the human heart. In the dog the chief initial deflections are usually in the same direction in the three conventional leads, and the experimental picture is termed concordant. In man, however, the electrocardiographic picture which typifies bundle branch block is usually of the discordant form, i. e., if the chief initial complex is upright in lead I, it is down in lead III, whereas in lead II it may be upright, down or biphasic. This difference is explained by the differences in the anatomic course of the left bundle branch, the axis and position of the heart, the shape of the heart and the thickness of the two ventricles.

In man the criteria established by Carter [5] (1914) for the diagnosis of bundle branch block were as follows: (1) widening of the QRS complex beyond 0.1 second, with notching; (2) preponderance of the ventricle with a healthy bundle branch, i. e., right or left axis deviation, as the case might be, or, in other words, the dextrocardiogram with left bundle branch block and the levocardiogram with right bundle branch block; (3) exaggeration of the amplitude of the ventricular deflections (QRS and T); (4) the T wave directed oppositely to the initial ventricular deflection. If the initial ventricular deflection was upright in lead I

4. Wilson, F. N., and Hermann, G. R.: An Experimental Study of Incomplete Bundle-Branch Block and of the Refractory Period of the Heart of the Dog, Heart **8**:229, 1921.

5. Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the Auriculoventricular Bundle: A Report of Twenty-Two Cases in Which Aberrant Beats Were Obtained, Arch. Int. Med. **13**:803 (May) 1914.

and downwardly directed in lead III, right bundle branch block was assumed to exist; if it was down in lead I and upright in lead III, left bundle branch block was predicated. The former was much more commonly observed in studies of patients than the latter. This concept was in perfect accord with contemporary concepts of ventricular preponderance and premature contractions.

As early as 1920, however, Fahr,[6] on purely theoretic grounds, expressed doubt as to the validity of the interpretation of bundle branch block, as well as the curves indicating ventricular preponderance, and suggested that the terms right and left should probably be interchanged. The same year Oppenheimer and Pardee[7] stated that they found the interrupting lesion in the branch opposite the one anticipated when they examined two hearts histologically.

In 1930 more serious doubt began to develop in America regarding the accuracy of interpretation as to which is the levocardiogram and which is the dextrocardiogram in the case of the human being when Barker, Macleod and Alexander[8] published curves exactly opposite to those previously obtained for animals. These writers were able by a fortunate circumstance to make electrocardiograms of extrasystoles (ectopic contractions) produced by stimulating directly the exposed heart of a human subject. Wilson and these original investigators[9] suggested that the common type of bundle branch block (formerly called right bundle branch block) is in reality due to obstruction of the excitation wave along the left bundle branch, whereas the unusual variety (the reverse picture electrocardiographically) is due to a block of the right bundle branch.

Later, Marvin and Oughterson[10] (1932) and Vander Veer[11] (1933) made similar observations on exposed human hearts and in general confirmed the results. However, Lundy and Bacon[12] (1933),

6. Fahr, G.: An Analysis of the Spread of the Excitation Wave in the Human Ventricle, Arch. Int. Med. **25**:146 (Feb.) 1920.

7. Oppenheimer, B. S., and Pardee, H. E. B.: The Site of the Cardiac Lesion in Two Instances of Intraventricular Heart Block, Proc. Soc. Exper. Biol. & Med. **17**:177, 1920.

8. Barker, P. S.; Macleod, A. G., and Alexander, J.: The Excitatory Process Observed in the Exposed Human Heart, Am. Heart J. **5**:720, 1930.

9. Wilson, F. N.; Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle-Branch Block, Am. Heart J. **7**:305, 1932.

10. Marvin, H. M., and Oughterson, A. W.: The Form of Premature Beats Resulting from Direct Stimulation of the Human Ventricles, Am. Heart J. **7**:471, 1932.

11. Vander Veer, J. B.: Premature Beats Produced by the Mechanical Stimulation of the Exposed Human Heart, Am. Heart J. **8**:807, 1933.

12. Lundy, C. J., and Bacon, C. M.: Premature Left Ventricular Beats from Electrical Stimulation of Exposed Human Heart, Arch. Int. Med. **52**:30 (July) 1933.

in the same type of experiments, found that when the apical region of the left ventricle was stimulated the extrasystoles confirmed the new conception but that when the basal region of the left ventricle was stimulated the major deflection was upright in lead I. Also, Prinzmetal, Oppenheimer and Dack [13] (1937), stimulating electrically the upper lateral region of the left ventricle of the exposed heart of a patient with constrictive pericarditis whose electrocardiograms showed right axis deviation due to displacement of the right ventricle forward and to the left, obtained extrasystoles with a small upright main complex in lead I and a large upright main complex in lead III; whereas, after closure, when they tapped the thin thoracic wall overlying the right ventricle at four different points, they found the main ventricular deflection of the resulting extrasystoles inverted in lead I and upright in lead III in 3 instances and the reverse in the fourth instance. These authors concluded that the new conception can be safely applied only in the presence of a normal electric axis or of left axis deviation. They were aided in this belief by experimental work performed on cats by Abramson and Weinstein [14] (1936), who showed that the direction of the major ventricular complex in lead I changes at a line of transition which does not strictly divide the left from the right ventricle and that a shift in this line of transition occurs with rotation of the heart and alteration of the electric axis.

Wilson, Macleod and Barker [9] (1932) soon fortified the new terminology which had been proposed by using semidirect leads for dogs in which one or the other bundle branch had been severed and by stimulating the ventricles separately with an exploring needle held close to the surface.

About the same time Roberts, Crawford, Abramson and Cardwell [15] (1932), in experiments in which they divided the bundle branches in cat hearts, obtained both concordant and discordant curves in which when the right bundle branch was cut the chief initial deflection was downward in both types, but in lead III the deflection was upward in the discordant type. After the left bundle branch was cut, exactly opposite results were obtained. These results indicated to them that the important lead to study for determining the location of the lesion is lead I.

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13. Prinzmetal, M.; Oppenheimer, B. S., and Dack, S.: Localization of Ventricular Extrasystoles in a Human Heart with Right Axis Deviation, J. A. M. A. **108**:620 (Feb. 20) 1937.

14. Abramson, D. I., and Weinstein, J.: A Basis for the Analysis of Variations in the Form of Electrocardiographic Curves Resulting from Experimental Premature Contractions, Am. J. Physiol. **115**:569, 1936.

15. Roberts, G. H.; Crawford, J. H.; Abramson, D. I., and Cardwell, J. C.: Experimental Bundle-Branch Block in the Cat, Am. Heart J. **7**:505, 1932.

By means of a method of analyzing the electrocardiogram by a fusion of the three leads into a single curve, or monocardiogram, Mann [16] (1931) was able to show that with right bundle branch block the electrocardiogram has an inverted main deflection in lead I, while with left bundle branch block the main deflection is upright in lead I. As early as 1920 Mann [17] had concluded that the original terminology for bundle branch block was incorrect.

In human beings for whom a diagnosis of bundle branch block had been made, Nichol [18] (1933) found that in instances in which the chief initial deflection was up in lead I and down in lead III (right bundle branch block, original terminology) the subclavian pulse was definitely delayed, and he concluded that the curves really signified left bundle branch block.

By means of serial precordial leads Wilson, Johnston, Hill, Macleod and Barker [19] (1934), for patients who showed electrocardiographic curves which were formerly said to typify left bundle branch block, obtained curves in which the lead from the right side of the precordium showed a late chief upstroke, whereas the lead from the left side of the precordium showed an early chief upstroke approximately synchronous with the peak of R in lead I. These curves were strikingly similar to those which they obtained by the same method of leading after section of the right bundle branch in dogs.

Wolferth and Margolies [20] (1935), by studying graphically the time relations of various events associated with right and left ventricular contraction shown by a series of patients whose electrocardiograms conformed rigidly to accepted criteria for the common type of bundle branch block, found that ejection from the left ventricle was significantly delayed. Checking the methods employed by Wolferth and his co-workers, Katz, Landt and Bohning [21] (1935) urged caution in draw-

16. Mann, H.: Interpretation of Bundle-Branch Block by Means of the Monocardiogram, Am. Heart J. **6**:447, 1931.

17. Mann, H.: A Method of Analyzing the Electrocardiogram, Arch. Int. Med. **25**:283 (March) 1920.

18. Nichol, A. D.: The Interpretation of Lead Inversion in Bundle-Branch Block, Am. Heart J. **9**:72, 1933.

19. Wilson, F. N., and others: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S-Deflections in Lead I, Am. Heart J. **9**:459, 1934.

20. Wolferth, C. C., and Margolies, A.: Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle-Branch Block: Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, Am. Heart J. **10**:425, 1935.

21. Katz, L. N.; Landt, H., and Bohning, A.: The Delay in the Onset of Ejection of the Left Ventricle in Bundle-Branch Block, Am. Heart J. **10**:681, 1935.

ing such definite conclusions and pointed out that an interval of more than 0.18 second from the beginning of the QRS complex to the onset of ejection of the left ventricle, as given by the rise of the subclavian arterial pulse, suggests the probable presence of delay or obstruction of the impulse along the left bundle branch but does not exclude the simultaneous presence of depression of function of the right bundle branch. They concluded that the direction of the QRS complex is determined by other factors besides the block and cannot be used to locate the bundle branch involved in cases of intraventricular block. They suggested describing intraventricular block as (1) a common bundle branch type, (2) an uncommon bundle branch type or (3) an indeterminate type.

Kountz, Prinzmetal, Pearson and Koenig [22] (1935) cut the bundle branches of revived human hearts and found that a lesion of the right bundle branch was characterized by a deflection that was downward in lead I and upward in lead III, and that section of the left bundle branch produced the opposite picture. Also, with the heart in normal position they found that extrasystoles were similar to those described by Barker, Macleod and Alexander.

By artificial stimulation of the endocardium of the ventricles of the dog, Marcou [23] (1936) regularly produced extrasystoles with images the reverse of those originally designated as showing premature contractions of the left and right ventricles; usually the curves were of the discordant type, but occasionally they were of the concordant type of Rothberger and Winterberg.[24]

Because of the mass of experimental evidence that has accumulated, most American cardiologists have accepted the new terminology for the classic electrocardiographic curves designated as typical of bundle branch block. There are still, however, many types of electrocardiographic curves suggestive of bundle branch block but not typical of either classic left or classic right branch block. These undoubtedly represent instances of intraventricular block, but the exact mechanism of their production and the pathogenic factors are in doubt.

Apparently most European cardiologists still use the original terminology. Rothberger [25] has been the main champion of this school of

22. Kountz, W. B.; Prinzmetal, M.; Pearson, E. F., and Koenig, K. F.: The Effect of Position of the Heart on the Electrocardiogram: I. The Electrocardiogram in Revived Perfused Human Hearts in Normal Position, Am. Heart J. **10**:605, 1935.

23. Marcou, I.: Experimental Extrasystoles Elicited Through Artificial Stimulation of the Endocardium of the Dog, Am. Heart J. **12**:301, 1936.

24. Rothberger, C. J., and Winterberg, H.: Experimentelle Beiträge zur Kenntnis der Reizleitungsstörungen in den Kammern des Saugetierherzens, Ztschr. f. d. ges. exper. Med. **5**:264, 1916.

25. Rothberger, C. J.: Zur Diagnose des Schenkelblocks, Ztschr. f. klin. Med. **123**:460, 1933.

thought. In 1933 he published an extensive dissertation on the subject in which as a result of numerous animal experiments and with the aid of Mahaim's [26] histologic studies he defended the original concept. However, he stated that the only way to settle the question to the satisfaction of all is by means of expert, systematic histologic studies of the entire conduction system of the hearts of patients whose electrocardiograms showed evidence of bundle branch block.

TYPES OF CURVES DESIGNATED BY VARIOUS AUTHORS AS INDICATING INTRAVENTRICULAR AND BUNDLE BRANCH BLOCK

Confusion exists with reference to the exact significance of various aberrant forms of the ventricular complex, although most of them are assumed to be due to intraventricular block. In 1911 Lewis [27] called attention to anomalous electric complexes accompanying the ventricular contractions of premature beats arising in the auricle in some cases. He said he considered these changes due to disturbances of conduction in the smaller branches of the conduction system and called the anomalous beats aberrant. He stated, "There seems every prospect that, if this hypothesis be correct, it will be possible ultimately to identify lesions which affect not only the main divisions, but the smaller branches of the auriculo-ventricular bundle. . . . The products of asphyxia probably act in a selective manner upon the special tissues which serve the function of conducting impulses from auricle to ventricle." In 1912 Mathewson [28] reported 4 cases in human beings of bundle branch block conforming to the criteria established by Carter [5] for this condition in 1914, when he reported 22 cases. Since that time numerous reviews of series of cases have been published, which will be briefly discussed later. The criteria established by Carter, already noted, were widely accepted and remained for many years the basis of the clinical diagnosis of bundle branch block.

In 1917 Oppenheimer and Rothschild [29] described an electrocardiographic curve of a different kind which they attributed to defects in intraventricular conduction due probably, in their opinion, to lesions of the finer ramifications of the conduction system, especially in the left ventricle. They coined the term arborization block. In this curve there is low rather than large amplitude of the ventricular complex, and

26. Mahaim, I.: Les maladies organiques du faisceau de His-Tawara, Paris, Masson & Cie, 1931.

27. Lewis, T.: Observations upon Disorders of the Heart's Action, Heart **3**: 279, 1911.

28. Mathewson, G. D.: Lesions of the Branches of the Auriculo-Ventricular Bundle, Heart **4**:385, 1912.

29. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement, J. A. M. A. **69**:429 (Aug. 11) 1917.

there is increased duration of the QRS complex, which is slurred or notched in its main deflection, while there is no constant directional relation between the QRS complex and the T wave. There were many adherents to this conception, but latterly the idea has been abandoned by most workers, and the exact anatomic cause of such conduction disturbances remains unsettled. In 1919 Willius [30] reported under the title "Arborization Block" a series of 138 cases in which this type of curve was obtained, but several years later he stated that he had concluded that the use of this anatomic term is not justified.

In 1919 Wedd [31] discussed the clinical significance of slight notching of the R wave as observed in 30 cases. He said he believed this change to be due to myocardial disease with defective conduction. Willius [32] (1920) said he considered notching and slurring of the QRS complex in isolated derivations of the electrocardiogram to be graphic entities probably indicative of local disorders of the ventricular myocardium affecting the conduction system.

In a classic paper entitled "Bundle Branch Block and Arborization Block," Wilson and Herrmann,[33] in 1920, on the basis of animal experiments and clinical studies said they had concluded that "complete bundle branch block produces characteristic changes in the form of the ventricular complex both in animals and in man." They said they considered Carter's criteria correct for man. They concluded further, however, as follows: "Delayed conduction of the impulse through the branches of the His bundle (incomplete bundle branch block) produces ventricular complexes which are transitional in form between the normal ventricular complex and complexes characteristic of complete bundle branch block." At the same time they found little experimental evidence to indicate that lesions of the subdivisions of the bundle branches or their arborizations are the cause of "arborization block."

From 1920 to 1930 little was accomplished in the furtherance of fundamental knowledge concerning disturbances of intraventricular conduction, although many fine articles were published on the clinical significance of the electrocardiographic curves described in the earlier years. As previously mentioned, there was no unanimity of opinion even in this period concerning the question of right and left as applied to curves in cases of bundle branch block. The experiments, in 1930,

30. Willius, F. A.: Arborization Block, Arch. Int. Med. **23**:431 (April) 1919.

31. Wedd, A. M.: The Clinical Significance of Slight Notching of the R-Wave of the Electrocardiogram, Arch. Int. Med. **23**:515 (April) 1919.

32. Willius, F. A.: Observations on Changes in Form of the Initial Ventricular Complex in Isolated Derivations of the Human Electrocardiogram, Arch. Int. Med. **25**:550 (May) 1920.

33. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**:153 (Aug.) 1920.

of Barker, Macleod and Alexander on the excitatory process observed in the exposed human heart stimulated greater effort to obtain more exact knowledge of conduction disturbances.

In 1931 Wilson, Macleod and Barker [34] attempted by analytic methods to show that the view of the aforementioned investigators that so-called right branch block was left branch block and vice versa was not necessarily in conflict with the hypothesis that the electric axis at a given instant points in the average direction in which the excitation process is spreading at the moment. "Both the dextrocardiogram and the levocardiogram, canine and human, are dominated by electrical effects produced by the ventricular septum. Preponderant hypertrophy of one ventricle increases the magnitude of the electrical effects produced by the opposite ventricle by increasing the mass of its septal wall without altering its lateral wall."

In 1932 Wilson, Macleod and Barker [9] showed that the order in which in human beings the two ventricles pass into the excited state in bundle branch block can be determined by means of serial precordial leads. These precordial leads are so taken that relative negativity of the exploring electrode produces an upward deflection. The chief upstroke signals the arrival of the excitation process at the epicardial surface of the subjacent portions of the ventricular wall. In cases of bundle branch block the upstroke is early when the exploring electrode is placed over the contralateral ventricle and late when it is placed over the homolateral ventricle. The time of the chief upstroke is measured with reference to the first ventricular deflection in lead I, which is taken simultaneously with each precordial lead. In cases in which the standard electrocardiograms exhibit all the features regarded characteristic of bundle branch block of the less common variety, the chief upstroke is early with leads from the left side of the precordium and late with leads from the right side. Later, the authors used a modification of their original method to study the electrocardiographic changes produced by high grade intraventricular block which did not display all the characteristics generally considered necessary for the diagnosis of bundle branch block. Their first study [35] (1934) was concerned with an attempt to locate the conduction defect responsible for curves of the standard electrocardiogram with a QRS interval measuring 0.12 second or more, a narrow R deflection and a broad S deflection in lead I, a narrow Q or S deflection synchronous with R in lead I, and a

34. Wilson, F. N.; Macleod, A. G., and Barker, P. S.: The Interpretation of the Initial Deflections of the Ventricular Complex of the Electrocardiogram, Am. Heart J. **6**:637, 1931.

35. Wilson, F. N.; Johnston, F. D.; Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, Am. Heart J. **9**:447, 1934.

broad upward deflection synchronous with S in the same lead. This curve ordinarily might be considered as indicative of bundle branch block of the rare type. The precordial leads from the right side of the precordium showed a late chief upstroke, while those from the left side showed an early chief upstroke, approximately synchronous with the peak of R in lead I. The curves were strikingly similar to those obtained by the same method of leading after section of the right branch of the bundle of His in dogs. They concluded therefore that these not uncommon curves represented right bundle branch block in man.

The same year (1934) Wilson, Johnston and Barker [36] studied similarly 3 patients who presented curves of a less common type, in which in lead I all the ventricular deflections were small, with a conspicuous S deflection and a usually flat or upright T wave, while in leads II and III the ventricular deflections were similar in all respects to those seen in cases of bundle branch block of the left, or common, variety. With the precordial lead the ventricular complex was found to be like those for dogs with right branch block and for patients with a diphasic ventricular complex of the rare type. They concluded that these curves represented right bundle branch block and that some additional factor might modify the form of the electrocardiogram. They pointed out that Mahaim [26] had studied histologically a case in which there was a similar electrocardiogram and had found, as the result of an infarct on the anterior and septal wall of the left ventricle, lesions interrupting the right branch and the anterior division of the left branch.[37] In figures 63, 72, 89, 95 and 100 of Mahaim's book the curves also showed a conspicuous S deflection in lead I, quite different from curves usually attributed to left bundle branch block.

Brown [38] (1936), from a study of esophageal and precordial leads, concluded that the common type of bundle branch block is the left, that bundle branch block does not necessarily give rise to "opposing T waves" and that right bundle branch block may be present in cases in which there are conventional curves of the common type and therefore likely occurs more often than is usually admitted under the new terminology. Two cases of the common type were probably of a "mixed" or "partial" variety. "Interpretations relying only on the basis of the directions of the main deflections in standard leads 1 and

36. Wilson, F. N.; Johnston, F. D., and Barker, P. S.: Electrocardiograms of an Unusual Type in Right Bundle-Branch Block, Am. Heart J. **9**:472, 1934.

37. Mahaim,[26] observation VI on page 242.

38. Brown, W. H.: A Study of the Esophageal Lead in Clinical Electrocardiography: I. The Application of the Esophageal Lead to the Human Subject with Observations on the Ta-Wave, Extrasystoles and Bundle-Branch Block, Am. Heart J. **12**:1, 1936.

3 are not always reliable in indicating the site of the responsible lesion in bundle branch block." The curves of ventricular extrasystoles supported the work also of the Wilson school.

Graybiel and Sprague,[39] in analyzing 395 cases of bundle branch block in 1933, outlined a classification, based purely on types of clinical curves:

1 (*A*). Left bundle branch block—homophasic type, in which the curves fulfil all the criteria of complete left bundle branch block [new terminology] except that the T wave and the QRS complex are similarly directed in lead I (26 cases)

1. (*B*). Left bundle branch block—heterophasic type, in which the curves fulfil all the classic criteria of complete left bundle branch block (99 cases)

2. Right bundle branch block—heterophasic type, in which the curves fulfil all the classic criteria of right bundle branch block (there was no instance of the homophasic type in the 29 cases)

3. Bundle branch block—indeterminate type, in which the T wave is often but not always oppositely directed to the QRS complex and the QRS complex is often similarly directed in leads I and III (81 cases)

4. Significant aberration of the ventricular complex (probably indicating slight degrees of intraventricular bundle branch block), in which the QRS wave is usually slurred and notched but its duration is slightly if at all prolonged and in which the direction of the T wave is variable (160 cases)

These authors excluded cases of marked axis deviation, which often gives curves resembling bundle branch block, and cases of so-called functional bundle branch block.

Bayley[40] (1934), following Wilson's school, classified the curves obtained in 70 cases of right bundle branch block as follows:

Group 1. These curves are obtained in cases of bundle branch block of the less common type, corresponding to group II of Graybiel and Sprague (14 cases).

Group 2. These curves are similar to those of group 1 except that in lead I the amplitude of the R spike is greater than that of the S deflection (23 cases).

Group 3. These curves show in lead I a ventricular complex similar in all respects to that in group 2, but in lead III the most conspicuous QRS deflection is a slender deep inverted spike, usually preceded by a small summit and invariably followed by a broad summit, the amplitude of this last deflection being less than that of the inverted spike (28 cases).

Group 4. In lead III of these curves the initial deflection is a small summit, which is followed, as in the curves in group 3, by a deep inverted spike. At its apex the inverted spike is narrow, but the ascending limb, after rising sharply, usually shows a pronounced notch, beyond which its ascent is gradual. The base of the inverted spike is therefore greatly broadened. In some instances this broad upward movement in lead III is absent, and the ascending limb returns quickly to the base line and does not leave it during the remainder of the QRS interval.

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39. Graybiel, A., and Sprague, H. B.: Bundle Branch Block: An Analysis of Three Hundred and Ninety-Five Cases, Am. J. M. Sc. **185**:395, 1933.

40. Bayley, R. H.: The Frequency and Significance of Right Bundle-Branch Block, Am. J. M. Sc. **188**:236, 1934.

The distinguishing feature of these curves is the absence of a broad upstroke at the end of the QRS interval in lead III. In lead I the QRS deflection is similar to that of groups 2 and 3, except that R is usually taller and broader and S less conspicuous. T is usually upright. Some of the curves of groups 3 and 4 might easily be confused with those that represent left bundle branch block, from which they may be differentiated by the presence of a conspicuous and broad S in lead I.

In Bayley's series there were only 103 cases of left bundle branch block, as compared with these 70 designated as representing right bundle branch block, a ratio indicating that right bundle branch block is far more common than had been supposed.

Edeiken and Wolferth [41] called attention, in 1934, to the clinical significance of the M-shaped or W-shaped QRS complex in lead II of the electrocardiogram, which they said is due probably to an abnormality of intraventricular conduction as a result of myocardial disease. The amplitude of the QRS complex in lead II does not exceed 5 mm. All the components of the complex are above the base line in the M-shaped complex and below the base line in the W-shaped complex. Occasionally there is a deflection either preceding or following the M-shaped or W-shaped part of the complex, opposite in direction to its associated M-shaped or W-shaped component. The duration of the M-shaped or the W-shaped part is at least 0.08 second.

Von Deesten and Dolganos,[42] in 1934, described a form of atypical bundle branch block with a favorable prognosis, characterized by (1) a prolonged QRS complex; (2) an R wave in lead I of moderate amplitude and short duration followed by a prolonged notched S wave of smaller amplitude; (3) an upright T wave in leads I and II; (4) a downward directed initial phase of the QRS complex in lead III, returning quickly to above the iso-electric line, where the curve is notched and prolonged, with the T wave in lead III directed downward, and (5) a QRS complex in lead II similar in most instances to that in lead I except for a lower amplitude. They stated that the localization of the lesion causing these curves is uncertain.

Wolferth and Wood [43] (1933) and later Roberts and Abramson [44] (1936) discussed electrocardiographic curves with a ventricular com-

41. Edeiken, J., and Wolferth, C. C.: Clinical Significance of the M- or W-Shaped QRS Complex in Lead II of the Electrocardiogram, Am. J. M. Sc. **188**: 842, 1934.

42. von Deesten, H. T., and Dolganos, M.: Atypical Bundle-Branch Block with a Favorable Prognosis, Am. J. M. Sc. **188**:231, 1934.

43. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients with Presumably Undamaged Hearts: Hypothesis of an Accessory Pathway of Auriculoventricular Conduction (Bundle of Kent), Am. Heart J. **8**:297, 1933.

44. Roberts, G. H., and Abramson, D. I.: Ventricular Complexes of the Bundle-Branch Block Type Associated with Short P-R Intervals, Ann. Int. Med. **9**:983, 1936.

plex typical of the bundle branch block associated with a short PR interval, similar to the curves in cases previously described by Wilson [45]; Wedd [46]; Hamburger [47]; Pezzi [48]; Wolff, Parkinson and White,[49] and Holzmann and Scherf.[50] In some instances factors producing inhibition of vagal influences or the administration of quinidine brought about a transition to normal. One theory for this mechanism is that an accessory pathway of auriculoventricular conduction, such as that described by Kent [51] between the right auricle and the right ventricle, might exist in these cases and permit an actual acceleration of the passage of the impulse from the auricle to a section of the ventricle.

REVIEW OF CLINICAL STUDIES OF PERMANENT BUNDLE BRANCH BLOCK [52]

A number of studies of series of clinical cases of bundle branch block have been made since 1912. In that year Mathewson [28] reported 4 cases, 3 of left bundle branch block and 1 of right bundle branch block. In the last case the impairment of conduction was functional rather than permanent, since the form of the curve changed in the same electrocardiogram. Carter's [5] report in 1914 included 22 cases and indicated the frequency of left bundle branch block as compared with that of right bundle branch block, of which there was only 1 case in the series. There was a large incidence of aortic valvular disease, and the serious prognosis regarding the conduction defect was suggested. Carter pointed out the frequent association of impaired auriculoventricular conduction, stating that the junctional tissues as a whole have special pathologic propensities. The cases fulfilled the rigid cri-

45. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. **16**:1008 (Dec.) 1915.

46. Wedd, A. M.: Paroxysmal Tachycardia, Arch. Int. Med. **27**:571 (May) 1921.

47. Hamburger, W. W.: Bundle-Branch Block, M. Clin. North America **13**: 343, 1929.

48. Pezzi, C.: Considerations pathogéniques sur quelques cas de rhythme septal et paraseptal permanents, Arch. d. mal. du cœur **24**:1, 1931.

49. Wolff, L.; Parkinson, J., and White, P. D.: Bundle-Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, Am. Heart J. **5**:685, 1930.

50. Holzmann, M., and Scherf, D.: Ueber Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, Ztschr. f. klin. Med. **121**:404, 1932.

51. Kent, A. F. S.: Observations on the Auriculo-Ventricular Junction of the Mammalian Heart, Quart. J. Exper. Physiol. **7**:193, 1914.

52. The new terminology of bundle branch block is used throughout this article, even when the author quoted used the old terminology.

teria he established but which in 1918 he [53] modified somewhat to include cases in which there was low voltage as indicating involvement of both branches or their arborizations. In bringing forth their concept of "arborization block," in 1917, Oppenheimer and Rothschild [29] reported a series of 14 cases, with necropsies, showing that the curves described usually indicated extensive chronic degenerative changes of the myocardium associated with a serious prognosis. Willius [30] (1919) collected reports of 138 similar cases, in 69.6 per cent of which death occurred within an average of eight and a half months. In this series chronic endocarditis was diagnosed in 35.5 per cent of the cases and exophthalmic goiter in 5 cases, the remainder of the conditions belonging to the so-called degenerative group.

Herrick and Smith [54] (1922) published a study of 35 cases of bundle branch block, of which 32 fulfilled criteria of left branch interruption. Only 6 patients were under 50 years of age. All the patients had symptoms and physical signs of cardiac weakness (severe in 17). Only 1 patient had definite chronic valvular disease, although 10 had had rheumatic fever. Eleven patients died within eighteen months. In 1 case the QRS complex changed from moderate amplitude with large notching to large amplitude with slight notching as the congestive failure advanced, and changes from typical bundle branch block to a more normal complex occurred as the patient improved. Six patients had impaired auriculoventricular conduction, and 5 had auricular fibrillation.

White and Viko [55] (1923) found records of 130 cases of intraventricular block among 3,219 cases in which electrocardiograms were made. In 41 cases there was the so-called complete type of bundle branch block; in the others there was aberration of the ventricular complex. The "complete" type was shown by 34 males and 7 females, and only 2 were under 40 years of age, the average age being 60 years. In 40 cases there was left bundle branch block. The etiologic factor was thought to be arteriosclerosis in 33 cases, rheumatic fever in 4 cases and syphilis in 3 cases. Angina pectoris occurred in 8 cases and congestive failure in 23. Hypertension was found in 24 cases. In 14 cases auriculoventricular block also was present, being complete in 2. Auricular fibrillation coexisted in 7 cases. Thirteen of the patients died of heart failure within one year. The data relating to the cases

53. Carter, E. P.: Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations, Arch. Int. Med. **22**:331 (Sept.) 1918.

54. Herrick, J. B., and Smith, F. M.: Clinical Observations on a Block of the Branches of the Auriculoventricular Bundle, Am. J. M. Sc. **164**:469, 1922.

55. White, P. D., and Viko, L. E.: Clinical Observations on Heart Block, Am. J. M. Sc. **165**:659, 1923.

in which there were lesser degrees of intraventricular block were strikingly similar. In this group of 89 cases there existed also auriculoventricular block in 20 (complete in 12) and auricular fibrillation in 15. These authors also found among the 3,219 patients 156 cases of auriculoventricular block, of which 27 were complete and 129 incomplete. In 15 of the cases of complete heart block there was evidence of intraventricular block, 3 with well marked bundle branch block; and in 19 of the cases of partial block there was intraventricular block also. The incidence of heart failure was greater in the cases of intraventricular block than in those of auriculoventricular block, especially heart failure of the anginal type. Angina pectoris was found about four times more often in cases of intraventricular block.

Hart [56] (1925), also using Carter's criteria, reported on 25 cases, in 23 of which there was left bundle branch block. All but 5 patients were under 50 years of age, and 16 died within a few months. All had advanced heart disease. There were 16 males and 9 females.

Talley and Reed [57] (1926) studied 28 cases. Only 1 patient was under 40 years of age, and the diagnosis was chronic myocarditis in 23 cases. Nineteen were males, and 9 were females. There were 20 cases of left, 3 of right, 1 of alternating right and left and 4 of partial right bundle branch block. In 6 cases there was impaired auriculoventricular block also and in 8 auricular fibrillation. Fifteen patients died within six months. Two patients were alive after four and a half years. Congestive failure was the common end.

Willius [58] (1926) collected reports of 105 cases of "complete" bundle branch block, of which 99 were cases of left bundle branch block. The youngest patient was 17 years old and the oldest 88, but 87 patients were over 50. There were 60 males and 45 females. In 93 per cent of the cases there was hypertensive and arteriosclerotic heart disease, but most of the patients were ambulatory. Angina pectoris was present in 31 cases, but a history of cardiac infarction was obtained in only 1 case. Dyspnea was noted in all cases. Auricular fibrillation existed in 4 cases and a prolonged PR interval in 3. Forty-three of 66 patients were dead of heart failure within fourteen months; 18 were living, 2 as long as six years afterward.

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56. Hart, T. S.: Block of the Branches of the Bundle of His: Clinical Notes on the Changes Following the Administration of Digitalis; Comments on the Levocardiogram, Dextrocardiogram and Bicardiogram, Arch. Int. Med. **35**:115 (Jan.) 1925.

57. Talley, J. E., and Reed, O. K.: A Study of Twenty-Eight Cases of Bundle-Branch Block, Am. Heart J. **1**:262, 1926.

58. Willius, F. A.: Clinical Features of Cases Exhibiting Electrocardiograms Conforming to Those of Experimental Complete Bundle-Branch Block, Am. Heart J. **1**:576, 1926.

In Cowan and Bramwell's [59] (1925) series of 24 cases 23 were so-called typical cases of left bundle branch block. All but 3 patients were over 40 years old, and there were 20 males and 4 females. The principal complaint was dyspnea in 13 cases and anginal pain in 8. Cardiac enlargement was present in 14. There were 10 cases of chronic valvular disease and 2 of congenital heart disease, and in the others there was evidence of arterial degeneration. The blood pressure was over 150 systolic in 10. Auricular fibrillation was present in 5 cases and auriculoventricular block in 1. In the latter case the patient first showed complete heart block without bundle branch block, and three months later the two arrhythmias combined. Another patient had at first only an inverted T wave in leads I and II and one year later had left bundle branch block after a sudden cardiac attack. One patient showed bundle branch block which after five months was much less pronounced. Fourteen patients had died, all within eighteen months and 11 within a year. Only 1 had been under observation for as long as four years.

Of Bach's [60] 80 patients (1930) 50 had degenerative heart disease, 17 had syphilitic heart disease and 11 had mitral stenosis. For those with degenerative heart disease the average age was 59 years, and 20 per cent of the patients died within a year. However, 1 patient was living after fourteen years, 1 after nine years and 23 after seven years. Nine of the syphilitic patients died at the average age of 45 years, whereas only 1 of the rheumatic patients was dead. Some patients, especially those with degenerative heart disease, showed a low voltage, with left axis deviation at first and later slight lengthening and notching of the QRS complex, and finally left bundle branch block.

Luten and Grove [61] (1929) presented a study of 237 cases which did not fulfil the commonly accepted criteria of bundle branch block but which the authors considered as instances of defective conduction in the right branch but which possibly they might now change to that of the left branch. The QRS complex was upright in lead I and the T wave inverted, whereas the QRS complex was downward in lead III and the T wave was upright, but the QRS interval was less than 0.1 second. The number of these cases in which a diagnosis of cardiac disease was given as the principal or secondary consideration amounted

59. Cowan, J., and Bramwell, J. C.: Clinical Aspect of Bundle-Branch Block, Quart. J. Med. **19**:95, 1925.

60. Bach, F.: On the Clinical Significance of Right Bundle Branch Block, Quart. J. Med. **23**:261, 1930.

61. Luten, D., and Grove, E.: The Incidence and Significance of Electrocardiograms Showing the Features of Left Axis Deviation and QRS of Normal Duration with Inverted T_1 and Upright T_3, Am. Heart J. **4**:431, 1929.

to only 56 per cent of the total number. Only 11 patients were under 35 years of age. Hypertension was present in 89 per cent of all cases and arteriosclerosis in 78 per cent. In 100 of the 132 cases of cardiac disease there was evidence of coronary arteriosclerosis, hypertensive heart disease or angina pectoris. There were 25 cases of syphilitic heart disease or aneurysm, 5 of rheumatic heart disease, 1 of "thyroid heart disease" and 1 of bacterial endocarditis. In only 6 of the remaining 102 cases was there neither arteriosclerosis nor hypertension. Cardiac hypertrophy was present in 110 cases (48 per cent) and probably in 97 others. Seven necropsies had been performed, and in all cases there was significant coronary arteriosclerosis.

In 39 of the 41 cases of classic bundle branch block studied by Hill [62] (1930) there was block of the left branch. All but 2 of the patients were over 40 years old, and there were 31 males and 10 females. All the patients had dyspnea, 15 had angina pectoris and 12 had edema. Hypertension was present in 15 cases, and aortic regurgitation in 4, and there was a rheumatic history in 3. Chronic valvulitis was present in some cases and toxic goiter in a few. The patients all died within a year or a little more. Auricular fibrillation occurred in 10 cases and auriculoventricular block in 5, with an increased PR interval in several others. Faint heart sounds and an apical systolic murmur were common.

Campbell and Turkington [63] published a study, in 1931, of 56 cases of left bundle branch block (they used the old terminology—right bundle branch block). All but 9 patients were over 40 years of age, and the average age was 58.6 years for hospitalized patients and 63.1 years for private patients. There were 36 males and 20 females. The cardiac diagnoses were not clearly stated, but there was a history of previous rheumatic infection in 9 cases, syphilis in 3 cases, bacterial endocarditis in 2 cases and definite peripheral arteriosclerosis in 14 cases. The blood pressure was over 150 systolic in 26 cases and over 200 systolic in 3 cases. Evidence of disease of the mitral valve was present in 34 cases and disease of the aortic valve in 8 cases. Dyspnea was noted in 43 cases, anginal pain in 22 cases, marked heart failure in 34 cases, edema in 15 cases and cardiac enlargement in almost all cases, being severe in 10 cases. Auricular fibrillation was noted in 4 cases. Thirty patients died within six years. Of the 22 patients known to be living, 4 were alive after nine years, 1 after thirteen years and another after seven years. The remainder lived less than three years.

62. Hill, I. G. H.: Bundle-Branch Block: A Clinical and Histological Study, Quart. J. Med. **24**:15, 1930-1931.

63. Campbell, S. B. B., and Turkington, S. I.: Right Bundle-Branch Block: An Analysis of the Clinical Records of Fifty-Six Cases with Typical Electrocardiograms, Quart. J. Med. **24**:481, 1931.

Smith's [64] (1932) 47 patients were all ambulatory when first seen. The youngest patient was 36 years old. There were 34 males and 13 females. All but 3 were dead after eighteen months. These 3 were living after three, four and five years, respectively.

The report of Tung and Cheer [65] (1933) from China was interesting because in 10 of the 16 cases there was right bundle branch block. One patient was 10 years old, another 11 and the others 28 or over. There were 11 males and 5 females. Seven of the patients with right branch block had rheumatic heart disease with mitral stenosis, 2 had coronary arteriosclerosis and 1 had congenital dextrocardia, with evidence of a patent septum. Of the patients with left bundle branch block, 5 had hypertension and 1 arteriosclerotic heart disease. Three patients with mitral stenosis first had preponderance of the right ventricle and later right bundle branch block. The authors suggested that many cases of ventricular preponderance are probably due, in part at least, to defective bundle branch conduction. They said they believed that dilatation and stress and strain of a ventricle are factors in producing intraventricular block.

Graybiel and Sprague [39] reported (1933) on a great series of 395 cases as an extension of the report of White and Viko [55] (1923). They classified their cases according to the types of curves, as already shown. There were 26 cases of left bundle branch block of homophasic type, 99 cases of left bundle branch block of heterophasic type, 29 cases of left bundle branch block of heterophasic type, 81 cases of right bundle branch block of heterophasic type, 160 cases of bundle branch block of indeterminate type and 109 cases in which there was found to be significant aberration of the ventricular complex. All but 45 patients were over 40 years of age, and 216 were between 40 and 70. There were 301 males and 94 females. Probable coronary arteriosclerosis was present in 238 cases, hypertension in 154, rheumatism in 47 and chronic pericarditis in 11. The heart was enlarged in 154 of 166 cases; mitral stenosis was present in 35 cases, mitral regurgitation in 36, aortic stenosis in 11 and aortic regurgitation in 49. There was evidence of definite coronary occlusion in 31 cases and of aortic aneurysm in 2. Auricular fibrillation existed in 54 cases, partial heart block in 20 and complete heart block in 17. Congestive failure occurred in 118 cases, angina pectoris in 59, Adams-Stokes attacks in 12, cardiac asthma in 12 and effort syndrome in 4. Of 308 patients followed, 85 were living

64. Smith, A. L.: Review of Forty-Seven Cases of One-Sided Branch Block, Nebraska M. J. **17**:179, 1932.

65. Tung, C. L., and Cheer, S. N.: A Correlation of Clinical and Electrocardiographic Findings in Human Bundle-Branch Block, Chinese M. J. **47**:15, 1933.

an average of two years and eleven months later, whereas 223 died within an average of fourteen months.

King [66] (1934) analyzed 155 instances of bundle branch block in 150 patients. There were 134 instances of left and 21 of right bundle branch block, although in 5 cases the block changed from one side to the other. The average age of the patients with "senile" heart disease was 61 years, of those with syphilitic heart disease 42 years and of those with rheumatic heart disease 42 years. There were 109 males and 41 females. The etiologic agents held responsible were arteriosclerosis (coronary) in 108, syphilis (aortic) in 14 and rheumatic fever (causing valvulitis) in 15, with a doubtful etiologic agent in 18. Auricular fibrillation occurred in 26 cases (22 cases of left and 4 cases of right branch block). Prolongation of the PR interval was observed in 28 cases and complete heart block in 36. The author showed that bundle branch block may be expected to occur in about 2 per cent of all patients suffering from syphilitic cardiovascular disease and in 5.5 per cent of all patients with rheumatic infection of various types. Of 104 patients traced, 76 were dead, the average duration of life after the diagnosis of bundle branch block was made being one year for the senile patients, ten and six-tenths months for the syphilitic patients and one year and eight months for the rheumatic patients. There were autopsies in 17 cases, with a close correlation between the clinical and the gross pathologic diagnosis.

Mention has previously been made of an "atypical bundle-branch block with a favorable prognosis" described by von Deesten and Dolganos [42] (1934). One patient was living after eleven and a half years, at the age of 72 years, and another after eight and a half years, at the age of 54 years.

Mention has also been made of the article by Edeiken and Wolferth [41] (1934) concerning cases in which there was an M-shaped or W-shaped QRS complex in lead II, which is apparently a manifestation of arteriosclerotic heart disease and often results from coronary occlusion.

Bayley [40] (1934) discussed the frequency and significance of right bundle branch block as observed at Ann Arbor, Mich. There were 70 cases, as compared with 103 cases of left bundle branch block, a much higher incidence than in any of the previous reviews by other authors. Bayley divided the cases of right branch block into four groups, which have already been described. He stated that the position of the heart, infarction in the septum or free wall of the left ventricle and preponderance of the left ventricle are probably the chief factors, absence or

66. King, J. T.: Bundle-Branch Block: A Case Analysis with Especial Reference to Incidence and Prognosis, Am. J. M. Sc. **187**:149, 1934.

presence of which, singly or in combination, accounts for the variation in form of the initial deflection in curves for patients with complete right bundle branch block. He found both right and left branch block to be considerably more common with arteriosclerotic heart disease than with other etiologic types. Often little or no evidence of cardiovascular disease was found on routine physical examination. "When patients with rheumatic heart and mitral stenosis develop bundle-branch block, the conduction defect is almost invariably on the right side."

Wood, Jeffers and Wolferth [67] (1935) reported a follow-up study of 64 patients with a defect of right bundle branch conduction. Because a large number of these patients had lived several years, the authors concluded that in the absence of other evidence of heart disease, bundle branch block is not necessarily an ominous sign. Three fourths of the patients were over 50 years of age when first seen. In 3 patients the block developed during observation; the first had practically no evidence of cardiovascular disease, the second had definite disease of the coronary artery and the third showed the deformity during a fatal attack of coronary occlusion. In 3 cases the QRS deformity appeared and disappeared from time to time. Twenty patients showed no evidence of heart disease when first seen, 13 showed relatively minor evidence and 17 showed definite evidence of heart disease.

Salcedo-Salgar and White [68] (1935) became interested in the relation of all forms of conduction block to clinical manifestations of disease of the coronary arteries. Only 8.8 per cent of 700 patients with angina pectoris showed heart block, either auriculoventricular (1.1 per cent) or intraventricular (7.3 per cent) or both (0.4 per cent), and only 13.1 per cent of 328 patients with coronary thrombosis showed heart block, either auriculoventricular (3.6 per cent) or intraventricular block (8.9 per cent) or both (0.6 per cent). Of 181 patients with intraventricular block of all grades, 29.8 per cent showed angina pectoris without clinical coronary thrombosis, and only 9.3 per cent showed coronary thrombosis, making a grand total of 46.9 per cent of the patients with intraventricular block with clear evidence of disease of the coronary arteries, as compared with 21.3 per cent of the patients with auriculoventricular block with the same evidence. A few over half of those with typical left bundle branch block and the same number of those with typical right bundle branch block had angina pectoris or coronary thrombosis or both. The prognosis for patients over 50 years

67. Wood, F. C.; Jeffers, W. A., and Wolferth, C. C.: Follow-Up Study of Sixty-Four Patients with a Right Bundle-Branch Conduction Defect, Am. Heart J. **10**:1056, 1935.

68. Salcedo-Salgar, J., and White, P. D.: The Relationship of Heart-Block, Auriculoventricular and Intraventricular, to Clinical Manifestations of Coronary Disease, Angina Pectoris, and Coronary Thrombosis, Am. Heart J. **10**:1067, 1935.

of age with either auriculoventricular or intraventricular block was about equally unfavorable whether or not there were associated clinical evidences of disease of the coronary arteries.

Sampson and Nagle [69] (1936) discussed the prognosis of bundle branch block as determined by a study of 157 cases conforming to Carter's criteria and the prognosis for a group of 112 heterogeneous examples of atypical block of the intraventricular conduction system. There were 146 cases of classic left bundle branch block and 11 cases of classic right branch block. The authors noted a high fatality during the first year after discovery of classic bundle branch block and a remarkable diminution of the fatality rate for patients who survived this period, some patients living as long as eleven years. The patients with atypical intraventricular block had about the same life expectancy after they reached the later decades, and some lived as long as sixteen years. Among the 157 patients with classic branch block there were 96 males and 61 females; among the 112 patients with intraventricular block there were 75 males and 37 females. All but 14 of the patients with classic block were 40 or more years of age, and all but 28 of those with atypical block were 40 or more years of age. Arteriosclerotic heart disease and arteriosclerotic combined with hypertensive heart disease comprised the etiologic factors in 108 of the cases of classic block and 58 of the cases of atypical block, approximately two thirds of each group. There were a total of 23 cases of syphilitic heart disease, 22 cases of rheumatic heart disease, 11 cases of thyrotoxic heart disease, 7 cases of congenital heart disease and 40 cases in which there were miscellaneous or doubtful etiologic factors.

As regards prognosis, Bishop and Bishop [70] (1932) suggested caution, since a patient with hypertensive heart disease with "complete" left bundle branch block was observed by them for eleven years and was well at the time of the report

As a rare cause of right bundle branch block Crawford and de Veer [71] (1932) described an aneurysm, 9 cm. in diameter, arising in the first portion of the aorta which produced marked stenosis of the pulmonary valve and projected into the right ventricle, with considerable damage to the interventricular septum. Serial sections, studied by Alfred E. Cohn, were not satisfactory. The authors referred to a similar case reported by Rothschild, Sacks and Libman, in 1927, and another reported

69. Sampson, J. J., and Nagle, O. E.: The Prognosis of Bundle-Branch Block and Other Intraventricular Conduction System Lesions, Am. J. M. Sc. **191**:88, 1936.

70. Bishop, L. F., and Bishop, L. F., Jr.: Bundle Branch Block of Unusual Duration, J. A. M. A. **98**:398 (Jan. 30) 1932.

71. Crawford, J. H., and de Veer, J. A.: Aneurysm of the Aorta Producing Pulmonary Stenosis and Bundle-Branch Block, Am. Heart J. **7**:780, 1932.

by Stejfa, in 1930. In the latter case the diagnosis of this unusual lesion was made ante mortem on the basis of a rough systolic murmur in the second and third left interspaces, with enlargement of the heart to the right and to the left and signs of aortic insufficiency accompanied with tracheal tug and paralysis of the left recurrent laryngeal nerve. The description of the study of the bundle branches was vague.

TRANSIENT, INTERMITTENT AND "FUNCTIONAL" BUNDLE BRANCH BLOCK

For many years it has been recognized that bundle branch block is not always a permanent phenomenon. Probably if electrocardiograms were made more often, the transient or intermittent nature of the block would be evident more frequently.

Transient or intermittent bundle branch block may occur without evidence of organic heart disease, in which event it is more likely to be designated functional bundle branch block. Such cases are rare, however, since in most instances there are definite indications of cardiac disease and the occurrence of bundle branch block even transiently is presumptive evidence of the presence of organic heart disease.

One form of intermittent and recurrent bundle branch block is assumed to be of purely functional origin and not dependent on heart disease. This is the syndrome of bundle branch block with a short PR interval in healthy young persons prone to paroxysmal tachycardia or auricular fibrillation. It was first described, in 1930, by Wolff, Parkinson and White,[49] although Wedd,[46] in 1921, reported a case of the same nature which he assumed, however, to be due to an auriculoventricular nodal rhythm. In such cases the reversion to a normal ventricular complex, with a longer (normal) PR interval, spontaneously or by vagal release after exercise or atropinization is often but not always a striking phenomenon. While this feature was present in some of the cases reported by Wolff, Parkinson and White and in the 2 reported by Tung[72] (1936), it did not exist in the cases reported by Holzmann and Scherf[50] (1932), Wolferth and Wood[43] (1933) and Roberts and Abramson[44] (1936). In the case reported by Roberts and Abramson the use of quinidine was followed by the appearance of a normal electrocardiogram. Also, at times there was spontaneous transition from the abnormal complex alone to alternate grouping of abnormal and normal complexes. Holzmann and Scherf and later Wolferth and Wood postulated the presence of a band of aberrant conduction tissue between the right auricle and the right ventricle and stated that the conduction wave passes not only through the bundle of His and its branches but also over this aberrant bundle. Reaching the right ventricle via the

72. Tung, C.: Functional Bundle-Branch Block, Am. Heart J. **11**:89, 1936.

usual route, the wave finds the ventricle already activated by the impulse which has passed down the aberrant bundle and therefore refractory. Although Kent [51] (1914) described such an aberrant bundle in animals, no one has yet demonstrated it in the heart of man.

Palmer and White [73] (1928) found 107 cases of aberrant ventricular response to an auricular premature beat (with a normal response to normal auricular stimuli) in 387 consecutive cases in which the electrocardiogram showed an auricular premature beat. Such an abnormal ventricular response is assumed to be due to temporary fatigue of one branch of the bundle of His. These aberrant complexes had been described previously by others (Lewis,[74] 1909 and 1911; Robinson,[75] 1915; White and Stevens,[76] 1916; Levy,[77] 1922; Stenström,[78] 1924).

Mentzingen [79] (1934) reported an unusual case, that of a woman aged 54 years who had vasomotor spasms of the hands. An electrocardiogram showed left bundle branch block, which disappeared when amyl nitrite was administered. The effect wore off in several minutes, with sudden shifts from complexes typifying bundle branch block to normal complexes, without changes in the PR interval or in the heart rate and without transitional forms.

An interesting association of intermittent bundle branch block (left) with pneumonia and hyperthyroidism due to exophthalmic goiter was reported by Lamb [80] (1933) in the case of a woman aged 27 years. The block was assumed to be due to the toxic effect of infection plus tachycardia. The aberrant complexes recurred, with subsequent exacerbations of the hyperthyroidism. At times the aberrant complexes were interspersed with normal complexes.

Lewis [74] (1909, 1 case; 1911, 2 cases) was apparently the first to describe transient bundle branch block in cases of organic heart disease.

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73. Palmer, R. S., and White, P. D.: The Clinical Significance of Aberrant Ventricular Response to Auricular Premature Beats and to Paroxysmal Auricular Tachycardia, Am. Heart J. **4**:153, 1928.

74. Lewis, T.: (*a*) Paroxysmal Tachycardia, the Result of Ectopic Impulse Formation, Heart **1**:262, 1909-1910; (*b*) footnote 27.

75. Robinson, G. C.: The Action of the Vagi on the Heart in Paroxysmal Tachycardia, Arch. Int. Med. **16**:967 (Dec.) 1915.

76. White, P. D., and Stevens, H. W.: Ventricular Response to Auricular Premature Beats and to Auricular Flutter, Arch. Int. Med. **18**:712 (Nov.) 1916.

77. Levy, R. L.: Clinical Studies of Quinidin, Arch. Int. Med. **30**:451 (Oct.) 1922.

78. Stenström, N.: An Experimental and Clinical Study of Incomplete Bundle-Branch Block, Acta med. Scandinav. **60**:552, 1924.

79. von Mentzingen, A.: Ueber einen Fall von funktionellem Verzweigungsblock, Klin. Wchnschr. **13**:1158, 1934.

80. Lamb, A. E.: Bundle-Branch Block in Hyperthyroidism, M. Times & Long Island M. J. **61**:234, 1933.

Since then many similar cases have been reported. The following list includes the names of most of the authors of such publications: Mathewson [28] (1912, 1 case in which both conduction methods were displayed in the same record); Carter [5] (1914, 1 case); Wilson [45] (1915, 1 case, showing four different rhythms and three different ventricular complexes produced by stimulation of the vagus nerve and abolished in favor of the normal rhythm by the administration of atropine); Robinson [81] (1916, 7 cases of temporary aberration of the ventricular complex following impairment of the functional state of the heart); Daniélopolu and Danulescu [82] (1921, 1 case in which ocular compression with or without atropine or epinephrine was said to cause bradycardia, auriculoventricular block and an atypical QRS complex); Daniélopolu and Danulescu [83] (1922, 1 case in which strong binocular compression with or without atropinization caused curves typical of bundle branch block to appear); Stenström [78] (1924, 3 cases of temporary failure of intraventricular conduction and 5 cases in which there was a single aberrant complex of supraventricular origin); Stenström [84] (1927, 3 cases of bundle branch block in which the block disappeared for periods spontaneously or with slowing of the heart rate by rest or vagal pressure); Leinbach and White [85] (1928, 1 case in which at first there was two to one right bundle branch block and later complete branch block); Samet [86] (1927, 1 case of intermittent auriculoventricular block, with normal duration of QRS and prolongation of QRS during sinus rhythm); Willius and Keith [87] (1927, 3 cases of intermittent incomplete bundle branch block); Wenckebach and Winterberg [88] (1927, 1 case of bundle branch block, with a prolonged PR interval, in which

81. Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, Arch. Int. Med. **18**:830 (Dec.) 1916.

82. Daniélopolu, D., and Danulescu, V.: Lésions latentes des branches du faisceau auriculo-ventriculaire, moyens de les déceler, Arch. d. mal. du cœur **14**: 529, 1921.

83. Daniélopolu, D., and Danulescu, V.: Trouble de conductibilité dans les branches du faisceau auriculo-ventriculaire provoqué chez l'homme normal par l'excitation du vague, Arch. d. mal. du cœur **15**:361, 1922.

84. Stenström, N.: Further Experience on Incomplete Bundle-Branch Block in Man, Acta med. Scandinav. **67**:353, 1927.

85. Leinbach, R. F., and White, P. D.: Two to One Right Bundle-Branch Block, Am. Heart J. **3**:422, 1928.

86. Samet, B.: Zur Kenntnis der intraventrikulären Leitungsstörungen, Wien. Arch. f. inn. Med. **14**:15, 1927.

87. Willius, F. A., and Keith, N. M.: Intermittent Incomplete Bundle-Branch Block, Am. Heart J. **2**:255, 1927.

88. Wenckebach, K. F., and Winterberg, H.: Die unregelmässige Herztätigkeit, Leipzig, Wilhelm Engelmann, 1927.

slight exercise produced two to one auriculoventricular block and a normal intraventricular conduction time); von Kapff [89] (1928, 1 case of transient bundle branch block); Barnes and Yater [90] (1929, 1 case of paroxysmal tachycardia and alternating incomplete right and left bundle branch block, with fibrosis of the myocardium in a young woman); Moore and Stewart [91] (1930, 1 case of right bundle branch block in a patient with uremia; the block disappeared after the intravenous injection of hypertonic dextrose solution); Slater [92] (1930, 1 case of three to one and four to one partial bundle branch block, which the author said was an instance of type 2 bundle branch block); Baker [93] (1930, 1 case of temporary bundle branch block occurring during tachycardia, with restoration of normal intraventricular conduction as the heart rate became slower or during the administration of oxygen); Kelly [94] (1930, 1 case of two to one right bundle branch block, which later became complete); Herrmann and Ashman [95] (1931, 3 cases in which there was sudden transition from complete bundle branch block to normal intraventricular conduction after the taking of a deep breath and the holding of it for from a few seconds to a minute [type 2] and 5 cases of high grades of partial bundle branch block in which with or without other mechanism or disturbances of rhythm there appeared at times a normal short QRS interval); Carter and McEachern [96] (1931, 1 case in which there were paroxysms of auriculoventricular block, with variable and incomplete bundle branch block but with complete bundle branch block during the phases of sinus rhythm); Katz, Hamburger

89. von Kapff, D. W.: Ueber einen Fall von Passageren Schenkel-Block, Klin. Wchnschr. **7**:357, 1928.

90. Barnes, A. R., and Yater, W. M.: Paroxysmal Tachycardia and Alternating Incomplete Right and Left Bundle-Branch Block with Fibrosis of the Myocardium, M. Clin. North America **12**:1603, 1929.

91. Moore, N. S., and Stewart, H. J.: The Disappearance of Intraventricular Heart Block Occurring in Uremia Following the Intravenous Injection of Hypertonic Glucose Solution, Am. Heart J. **5**:469, 1930.

92. Slater, S. R.: Partial Bundle-Branch Block: A Case of Three-to-One and Four-to-One Block, Am. Heart J. **5**:617, 1930.

93. Baker, B. M., Jr.: The Effect of Cardiac Rate and the Inhalation of Oxygen on Transient Bundle Branch Block, Arch. Int. Med. **45**:814 (May) 1930.

94. Kelly, L. W.: Two-to-One Right Bundle-Branch Block, Am. Heart J. **6**:285, 1930.

95. Herrmann, G., and Ashman, R.: Partial Bundle-Branch Block: A Theoretical Consideration of Transient Normal Intraventricular Conduction in the Presence of Apparently Complete Bundle-Branch Block, Am. Heart J. **6**:375, 1931.

96. Carter, E. P., and McEachern, D.: Recurrent Complete Heart-Block: Report of a Case Associated with Transient Bundle-Branch Block and Normal Conduction Between Attacks, Bull. Johns Hopkins Hosp. **49**:337, 1931.

and Rubinfeld[97] (1932, 1 case in which a changing ventricular rate caused the appearance of transient bundle branch block of one type superimposed on that of the opposite type, with at times an alternation between the two after injection of epinephrine); Elliott and Nuzum[98] (1932, 1 case of left bundle branch block, with transient and spontaneous two to one auriculoventricular block during which the bundle branch block disappeared, and with later persistence of the bundle branch block except during slowing from vagal pressure [type 2]); Morris and McGuire[99] (1932, 2 cases of transient complete bundle branch block of acute onset with circulatory failure); Campbell and Suzman[100] (1932, 1 case in which there was gradual disappearance of bundle branch block, probably owing to coronary thrombosis); Sigler[101] (1933, 1 case in which stimulation of the left vagus nerve, paradoxically, removed the bundle branch block, and in which an abnormal QRS complex occurred after as long a rest period as 0.56 second, a normal complex being restored by an additional rest of 0.08 second); Pescador and Villanueva[102] (1932, 1 case of "functional" bundle branch block); Carr[103] (1933, 1 case in which the bundle branch block at first could be terminated by vagal stimulation but which later became permanent); Bagnaresi[104] (1934, 1 case of paroxysmal tachycardia, with polymorphism of the ventricular complex and typical bundle branch block); Willius and Anderson[105] (1934, 1 case of transient recurrent complete bundle branch block); Kurtz[106] (1936, 6 cases of transient bundle branch block, in 2 of which the occurrence of the block was closely

97. Katz, L. N.; Hamburger, W. W., and Rubinfeld, S. H.: Partial Bundle-Branch Block, Am. Heart J. **7**:753, 1932.

98. Elliott, A. H., and Nuzum, F. R.: Bundle-Branch Block with Periods of Normal Intraventricular Conduction: Report of an Unusual Case, Am. Heart J. **7**:680, 1932.

99. Morris, R. S., and McGuire, J.: Transient Complete Bundle-Branch Block, Am. J. M. Sc. **184**:202, 1932.

100. Campbell, M., and Suzman, S. S.: Simultaneous Disappearance of Gallop Rhythm and Bundle-Branch Block, Lancet **1**:985, 1932.

101. Sigler, L. H.: Functional Bundle-Branch Block (Partial) Paradoxically Relieved by Vagal Stimulation, Am. J. M. Sc. **185**:211, 1933.

102. Pescador, L., and Villanueva, S.: Un caso de pulso alternante por extrasístoles ventriculares derechos, simulando un bloqueo functional de la rama izquierda del fascículo de His, Med. ibera **1**:642, 1932.

103. Carr, F. B.: Functional Bundle Branch Block, New England J. Med. **209**:1101, 1933.

104. Bagnaresi, G.: Il blocco di branca instabile, Cuore e circolaz. **18**:65, 1934.

105. Willius, F. A., and Anderson, M. J.: Transient, Recurrent Complete Bundle-Branch Block, Am. Heart J. **10**:248, 1934.

106. Kurtz, C. M.: Transient Complete Bundle-Branch Block, Am. Heart J. **11**:212, 1936.

associated with periods of myocardial failure; in another case, block was present for a time after coronary occlusion.[106a]

It is probable that in such cases as most of those mentioned there are partial lesions of one or both bundle branches without complete interruption of function except when toxic or metabolic factors further compromise the conduction tissues or when release of vagal tone increases the heart rate. The onset may be abrupt, as when due mainly to a sudden insult, such as infarction, with gradual disappearance of the block, during the latter part of which period there may be frequent transitions; or the onset may be gradual, with or without more or less frequent transitions due to progressive involvement of the branch, or the transitions may occur with great frequency, regularly or irregularly, in cases in which the pathologic process may be relatively stationary, in which event the heart rate may be of greatest importance in the production of the transition. Similar factors are at work in cases of auriculoventricular heart block, in which for days, months or years the degree of block may be variable.

SUDDEN ONSET OF PERMANENT BUNDLE BRANCH BLOCK

A few cases have been observed in which permanent bundle branch block was noted to occur suddenly. It is a fortunate chance that affords such an observation. In Perry's[107] case (1934) the exact cause of the sudden change from a normal complex to that of bundle branch block could not be ascertained with certainty but was assumed to be slow coronary thrombosis in a case in which the bundle branch was already compromised. Another case, 1 of the cases reported by Hollingsworth[108] (1937), was that of a man whose electrocardiographic curve suddenly changed to that typical of bundle branch block while the electrocardiogram was being made and remained constant from then on. At the time of this abrupt transition there was no change in the patient's clinical condition.

PROGRESSIVE BUNDLE BRANCH BLOCK

In most cases of established bundle branch block the condition is probably progressive from sinus rhythm to complete block of the branch, as in most cases the etiologic factor is undoubtedly coronary

106a. Since this paper went to press an excellent article by Comeau, Hamilton and White has appeared (Comeau, W. J.; Hamilton, J. G. M., and White, P. D.: Paroxysmal Bundle-Branch Block Associated with Heart Disease, Am. Heart J. **15**:276, 1938). Another case has also been reported, by Bishop (Bishop, L. F., Jr.: Transient, Recurrent, Complete Left Bundle-Branch Block, ibid. **15**:354, 1938).

107. Perry, C. B.: Observed Onset of Bundle-Branch Block with Coronary Thrombosis Forty-Five Hours Later, Am. Heart J. **9**:642, 1934.

108. Hollingsworth, E. W.: Personal communication to the author.

arteriosclerosis and the lesions of the bundle branches are gradual to the point of complete destruction at one or more points. Such progression has been observed in many cases. An illustrative case is that reported by Krumbhaar [109] (1917, case 3), in which progressive establishment of bundle branch block was noted, with the occurrence of occasional aberrant beats during the different stages. Other instances were those reported by Hyman and Parsonnet [110] (1930). These authors described 5 cases, 4 of which began with the curve typical of left axis deviation and an inverted T wave in lead I and later changed to the curve typical of left bundle branch block and 1 of which began with the curve of right axis deviation and later changed to the curve typical of right bundle branch block. In the first case the sinus rhythm persisted; in the second case auricular fibrillation developed with the block of the branch; in the third case complete auriculoventricular block appeared with the bundle branch block complex; and in the fourth case extrasystoles arising from multiple foci occurred after the establishment of bundle branch block. Willius [111] (1933) described several cases of progressive myocardial disease in which the electrocardiogram showed progressive change to bundle branch block. In his third case the first tracings showed "left ventricular preponderance"; nine months later the T wave in lead I was inverted, and the QRS wave was slightly notched and showed a duration of 0.12 second; four months after this the changes were more marked, and necropsy showed marked coronary arteriosclerosis and myofibrosis. In his fifth case the first electrocardiogram showed "left ventricular preponderance," with an inverted T wave in lead I; the second tracing, made nine months later, showed inversion of the T wave in leads I and II, and one year after this the curves were typical of left bundle branch block. His sixth case was one of acromegaly with hyperthyroidism and cardiac hypertrophy, in which the first tracing showed "left ventricular preponderance" and the second tracing made four months after subtotal thyroidectomy showed typical left bundle branch block, the patient being then more dyspneic.

BUNDLE BRANCH BLOCK ASSOCIATED WITH IMPAIRED AURICULOVENTRICULAR CONDUCTION

Many cases are on record in which the form of the ventricular complex in the presence of auriculoventricular block was of the bundle branch type. In a number of these cases tracings made at different

109. Krumbhaar, E. B.: Transient Heart-Block: Electrocardiographic Studies, Arch. Int. Med. **19**:750 (May) 1917.

110. Hyman, A. S., and Parsonnet, A. E.: Bundle Branch Block: The Phenomenon of Its Development in Relation to Axis Deviation of the Heart, Arch. Int. Med. **45**:868 (June) 1930.

111. Willius, F. A.: The Progression of Myocardial Disease as Recorded by Serial Electrocardiograms, M. Clin. North America **16**:1493, 1933.

times or the same tracing showed shifts, abrupt or gradual, in the form of the ventricular complex from that of right to that of left bundle branch block or intermediate forms. In some of these cases the idioventricular rhythm was rapid, indicating probably an irritative as well as a destructive lesion in the branch in which the new automatic pacemaker was located.

In the section entitled "Review of Clinical Studies of Permanent Bundle Branch Block" the number of cases of bundle branch block associated with auriculoventricular block was noted in each series of cases in which the author included this feature in his report. Cornell, Claytor and I [112] (1936) have reviewed this subject, listing the reports of such cases obtained from the literature and reporting 3 cases of our own, with detailed histopathologic studies. We concluded that the pathogenic factor in all these cases is probably disease of the coronary arteries and that the condition is due usually to lesions, partial or complete, in both bundle branches in most instances, although we considered that destructive lesions of the terminal portion of the bundle of His may also produce such varying ventricular complexes. We stated that in cases of auriculoventricular heart block due to bilateral bundle branch lesions the form of the ventricular complex is frequently suggestive of bundle branch block and that variation in the form of this complex is common.

These variations suggest a shift in the site of the pace-maker, sometimes from one side of the septum to the other. The ventricular complexes may be of supraventricular form, however; and then there are either two pace-makers, one in each bundle branch, generating impulses simultaneously, or, more probably, a single pace-maker in one or the other branch sending impulses directly through the interventricular septum into the Purkinje network of the contralateral ventricle as well as into that of the homolateral ventricle.

VENTRICULAR PREPONDERANCE, VENTRICULAR STRAIN AND EFFECT OF CARDIAC POSITION ON THE ELECTROCARDIOGRAM

Since Lewis [113] (1914) and Cotton [114] (1917) first studied the effect of ventricular hypertrophy on the electric axis of the electrocardiogram a number of other excellent studies have been made (Bridgman,[115] 1915; Carter, Richter and Greene,[116] 1919; Pardee,[117] 1920;

112. Yater, W. M.; Cornell, V. H., and Claytor, T.: Auriculoventricular Heart Block Due to Bilateral Bundle-Branch Lesions: Review of the Literature and Report of Three Cases with Detailed Histopathologic Studies, Arch. Int. Med. **57**:132 (Jan.) 1936.

113. Lewis, T.: Observations upon Ventricular Hypertrophy, with Especial Reference to Preponderance of One or Other Chamber, Heart **5**:367, 1913-1914.

114. Cotton, T. F.: Observations upon Hypertrophy, Heart **6**:217, 1917.

115. Bridgman, E. W.: The Value of the Electrocardiogram in the Diagnosis of Cardiac Hypertrophy, Arch. Int. Med. **15**:487 (March) 1915.

(Footnotes continued on next page)

Dieuaide,[118] 1921; Herrmann and Wilson,[119] 1922; White and Burwell,[120] 1924; Reid, [121] 1928; Wilson and Herrmann,[122] 1930; Master,[123] 1930; Proger and Davis,[124] 1930). Ventricular preponderance, ventricular strain and the effect of the cardiac position on the electrocardiogram are subjects that have somewhat beclouded the subject of bundle branch block or disturbances of intraventricular conduction. This is true more particularly in cases in which there is slight prolongation of the QRS complex and in cases in which there is negativity of the T wave. In this connection the conclusions of Herrmann and Wilson [119] (1922) are worthy of quotation:

> The relative weight of the two ventricles is but one of many factors which influence the form of the ventricular complex of the electrocardiogram. Its influence predominates only when the heart is greatly hypertrophied. There is no definite relation between the form of the ventricular complex and the relative weight of the two ventricles when the ventricular weight is below 250 grams. The chief factors which disturb the relation between the form of the electrocardiogram and the relative weight of the two ventricles, so it is suggested, are: (1) variations in the position of the heart, (2) variations in the arrangement of the ventricular conducting system, and (3) disturbances of intraventricular conduction. The form of the normal electrocardiogram is not determined by the relative weight of the two ventricles: it is chiefly dependent upon the position of the heart and upon the arrangement of the ventricular conducting system; sometimes one, sometimes the other, of these factors exerts the greater influence.

In a later study Wilson and Herrmann [122] (1930) made further observations on this problem, with the following conclusions:

> Comparison of the QRS interval and the ventricular weight indicates that the length of this interval increases in average value with the cube root of the

116. Carter, E. P.; Richter, C. P., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, Bull. Johns Hopkins Hosp. **30**:162, 1919.

117. Pardee, H. E. B.: The Determination of Ventricular Predominance from the Electrocardiogram, Arch. Int. Med. **25**:683 (June) 1920.

118. Dieuaide, F. R.: The Determination and Significance of the Electrical Axis of the Human Heart, Arch. Int. Med. **27**:558 (May) 1921.

119. Herrmann, G. R., and Wilson, F. N.: Ventricular Hypertrophy: A Comparison of Electrocardiographic and Post-Mortem Observations, Heart **9**:91, 1922.

120. White, P. D., and Burwell, C. S.: The Effects of Mitral Stenosis, Pulmonic Stenosis, Aortic Regurgitation and Hypertension on the Electrocardiogram, Arch. Int. Med. **34**:529 (Oct.) 1924.

121. Reid, W. D.: Comparison of the Electrical Axis Shown by the Electrocardiogram with Roentgen Mensuration of the Heart, Am. Heart J. **4**:223, 1928.

122. Wilson, F. N., and Herrmann, G. R.: Relation of QRS-Interval to Ventricular Weight, Heart **15**:135, 1930.

123. Master, A. M.: Characteristic Electrocardiograms and Roentgenograms in Arterial Hypertension, Am. Heart J. **5**:291, 1930.

124. Proger, S. H., and Davis, D.: The Significance of Axis Deviation in the Human Electrocardiogram, Arch. Int. Med. **45**:975 (June) 1930.

ventricular weight. Comparison of the QRS interval and the thickness of the left ventricular wall shows a similar increase in the average value of this interval with an increase in muscle thickness. QRS intervals which exceed 0.10 second should not in general be ascribed to increased size of the heart or to increased thickness of the left ventricular wall alone, but to retarded intraventricular conduction.

The occasional observations, some of which have previously been alluded to, of the progression of the electrocardiographic picture of left axis deviation, with or without a slightly prolonged QRS interval and with or without inversion of the T wave in lead I, to the typical electrocardiographic picture of bundle branch block add considerable support to the conclusions of these authors.

The excellent paper of Barnes and Whitten[125] (1929) entitled "Study of T-Wave Negativity in Predominant Ventricular Strain" fails to take into account the possibility of lesions of the bundle branches in producing negativity of the T wave. These authors have shown that "in cases in which the strain was thrown predominantly on the left ventricle" there was often inversion of the T wave in lead I or in leads I and II; that "in cases in which the condition produced disproportionate load on the right ventricle" the T wave was often inverted in leads II and III, and that "in conditions in which multiple lesions compete for maximal strain on the two ventricles, the leads in which the T waves will be inverted cannot be predicted." These conclusions, logical as they seem, for the very reason that no account is taken of the influence of possible lesions of the bundle branches, indicate the need for more extensive study of the histologic structure of the conduction system in cases of negativity of the T wave.

The effect of the position of the heart on the form of the electrocardiogram has been studied by many authors since Einthoven and associates'[126] original publication on the subject in 1913. Noteworthy studies of this subject have been those of Waller[127] (1914); White and Bock[128] (1918); Cohn[129] (1922); Meek and Wilson[130] (1925);

125. Barnes, A. R., and Whitten, M. B.: Study of T-Wave Negativity in Predominant Ventricular Strain, Am. Heart J. **5**:14, 1929.

126. Einthoven, W.; Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. **150**:275, 1913.

127. Waller, A. D.: The Various Inclinations of the Electrical Axis of the Human Heart: 1A. The Normal Heart; Effects of Respiration, Proc. Roy. Soc., London, s.B **88**:49, 1914.

128. White, P. D., and Bock, A. V.: Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, Am. J. M. Sc. **156**:17, 1918.

(Footnotes continued on next page)

Jones and Roberts [131] (1929); Ackerman and Katz [132] (1933); Kissin, Ackerman and Katz [133] (1933); Kountz, Prinzmetal, Pearson and Koenig [22] (1935), and Alexander and Bauerlein [134] (1936), from which it may be concluded that, while the position of the heart affects the form of the electrocardiogram, mainly in regard to its electric axis, this factor is of little practical significance in connection with the curves in cases of bundle branch block, provided there is no extensive juxtacardiac lesion which would greatly alter the position of the heart and provided the patient is in the ordinary sitting or supine position during the making of the electrocardiogram.

The important questions arising out of these observations are: When is right or left axis deviation with a slightly prolonged QRS interval indicative of early bundle branch lesions, provided the position of the heart is normal? Is the additional presence of negativity of the T wave a definite sign of disturbance of function of a bundle branch? These questions can be answered only after extensive histopathologic study of the conduction systems of many hearts.

HISTOPATHOLOGIC STUDIES OF BUNDLE BRANCH BLOCK REPORTED IN THE LITERATURE

Thus far I have discussed bundle branch block purely from the standpoint of the experimental evidence of its nature and the electrocardiographic and clinical manifestations. Just as the concept from this point of view has varied so much, likewise the data concerning the histopathologic basis of this problem have been conflicting, incomplete and relatively scanty. Much less certainty, in fact, exists on this point because of the tremendous amount of labor required in the histologic study of the conduction system of one heart, the technical difficulties involved and the amount of experience necessary for evaluation of

129. Cohn, A. E.: An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, Heart **9**:312, 1922.

130. Meek, W. J., and Wilson, A.: The Effect of Changes in Position of the Heart on the QRS Complex of the Electrocardiogram, Arch. Int. Med. **36**:614 (Nov.) 1925.

131. Jones, H. W., and Roberts, R. E.: The Electrical Axis of the Heart As an Indication of Changes in Ventricular Predominance, Quart. J. Med. **23**:67, 1929.

132. Ackerman, W., and Katz, L. N.: Reversal in Direction of the QRS Complex of Experimental Right Bundle-Branch Block with Change in the Heart's Position, Am. Heart J. **8**:490, 1933.

133. Kissin, M.; Ackerman, W., and Katz, L. N.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Bundle-Branch Block in Man, Am. J. M. Sc. **186**:721, 1933.

134. Alexander, H. L., and Bauerlein, T. C.: The Influence of Posture on Partial Heart-Block, Am. Heart J. **11**:223, 1936.

the findings. Few persons have had extensive experience in this field of research, and even their conclusions are extremely at variance.

For a study of every portion of the microscopically recognizable portion of the conduction system usually between 4,000 and 6,000 serial sections are required depending mainly on the size of the heart. Furthermore, in order for the reader to be able to judge of the merits of the work, not only must the writer carefully describe his findings, but he should also reproduce photomicrographs and electrocardiograms.

A careful review of the literature up to 1930 by Mahaim [26] revealed reports of only 19 cases involving the electrocardiographic diagnosis of bundle branch block in which anatomic studies had been made. Mahaim considered only 3 of these cases sufficiently well studied histologically to be accepted as convincing (Eppinger and Stoerk,[135] 2 cases, 1910; Kauf,[136] 1 case, 1924) and a fourth case as probably correctly evaluated (Fredericia and Möller,[137] 1918). The authors stated that lesions were observed in the right bundle branch and not in the left; the electrocardiograms had shown right bundle branch block, according to the original terminology. Even with Mahaim's rigid criteria, these 4 cases are open to criticism. The 2 cases of chronic aortic valvulitis with congestive failure reported by Eppinger and Stoerk were presented without photomicrographs and with only brief histologic descriptions; furthermore, the left bundle branch was said to be entirely unaffected in both—the correctness of this statement is doubtful, since it must be rare to find one branch seriously diseased without some involvement of the other. Kauf's case was also one of disease of the aortic valves (stenosis with calcification); the description of the microscopic study was brief, and the left bundle branch was said to be entirely normal. In the case of degenerative heart disease reported by Fredericia and Möller there had been frequent changes in the form and direction of the ventricular complex but no curve showing definite bundle branch block of either side. The authors described briefly marked fibrosis of the left bundle branch but none of the right, a remarkable observation in view of the electrocardiographic features.

Among the 15 other cases reviewed by Mahaim, there were 3 in which a histologic study of the conduction system was not made (2 cases reported by Lutembacher [138] [1926] apparently of coronary arterio-

135. Eppinger, H., and Stoerk, O.: Zur Klinik des Elektrokardiogramms, Ztschr. f. klin. Med. **71**:157, 1910.

136. Kauf, E.: Zur Diagnose des Schenkelblocks beim menschlichen Herzen, Ztschr. f. klin. Med. **98**:126, 1924.

137. Fredericia, L. S., and Möller, P.: Ein Fall von auf das Septum lokalisierter Myocarditis mit eigentümlichen Abnormitäten im Elektrokardiogramm, Deutsches Arch. f. klin. Med. **126**:247, 1918.

138. Lutembacher, R.: Coronarite et infarctus sous-endocardiques à forme embolique, Arch. d. mal. du cœur **19**:505, 1926; Coronarite et artérites du pancréas; troubles de conduction et diabète, ibid. **19**:522, 1926.

sclerosis, both including disturbance of auriculoventricular conduction and 1 case of right and the other of left bundle branch block; 1 case reported by Parkinson and Bedford [139] [1928] of multiple myocardial infarcts, with the electrocardiographic curve showing left bundle branch block).

Four cases reported by Carter [5] were incompletely studied histologically by Cohn and Lewis [140] (1914) largely because the tissue which was sent them was not adequate. In the case of chronic aortic and mitral valvulitis reported by von Wyss [141] (1911) and studied histologically by Gerhardt,[142] there were disturbances of auriculoventricular conduction, with the curve typical of left bundle branch block, but only one lead of the electrocardiogram was reproduced; Gerhardt observed partial lesions of both branches. The findings were therefore inconclusive.

Carter,[53] in 1918, revised his ideas somewhat concerning bundle branch block, as the result of a study of a case in which the electrocardiographic complexes were similar to those described by Oppenheimer and Rothschild [29] as indicative of arborization block. In general the curve resembled that typical of right bundle branch block but with low amplitude except during paroxysms of tachycardia, when the amplitude was high. The histologic study, made by van der Stricht, was not complete, since only a number of isolated blocks of tissue were examined. These showed localized areas of fibrosis in the main stem and in the posterior division of the left bundle branch.

The 2 cases reported by Oppenheimer and Pardee [7] (1920) were described in abstract form with extremely little detail and no illustrations. One was said to be a case of left bundle branch block with lesions confined to the right bundle branch, and the other was said to be a case of right bundle branch block with lesions confined to the left bundle branch. From these data the authors questioned the accuracy of interpretation of electrocardiograms in cases of bundle branch block.

Drury [143] (1921) made an incomplete histologic study of a case of auricular flutter in which the curve was suggestive of right bundle branch block of low voltage, owing to chronic coronary occlusion.

Waldorp's [144] case (1924) can hardly be called one of bundle branch block, and the histologic study was not convincingly described.

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139. Parkinson, J., and Bedford, E.: Cardiac Infarction and Coronary Thrombosis, Lancet **1**:4, 1928.

140. Cohn, A. E., and Lewis, T.: The Pathology of Bundle Branch Lesions of the Heart, Proc. New York Path. Soc. **14**:207, 1914.

141. von Wyss, W.: Beiträge zur der Klinik des Elektrokardiogramms, Deutsches Arch. f. klin. Med. **103**:505, 1911.

142. Gerhardt, D.: Klinische und anatomische Beiträge über Adams-Stokes'sche Krankheit und Vagusbradykardie, Deutsches Arch. f. klin. Med. **106**:462, 1912.

143. Drury, A.: Arborization Block, Heart **8**:23, 1921.

144. Waldorp, C. P.: Bradyarrythmie dans une fibrillation auriculaire, Rev. Asoc. méd. argent. **37**:74, 1924.

Wenckebach and Winterberg[145] (1927) described a case of intermittent auriculoventricular heart block of varying degree in which there were variable ventricular complexes, the complex indicative of right bundle branch block predominating. The histologic study showed multiple lesions of the left bundle branch; the right branch could not be studied because of technical difficulties.

Marvin[146] (1928) described a case of left bundle branch block with tachycardia in which, after overdosage of digitalis, crises of polymorphic ventricular tachycardia of the alternating type occurred. The histologic study of the large, probably hypertensive, heart was incomplete.

The case reported by Taussig[147] (1929) cannot properly be called one of left bundle branch block because the electrocardiogram showed ventricular tachycardia. Also, the histologic study was incomplete.

Agostoni[148] (1929) studied a case in which the electrocardiogram showed left bundle branch block. By studying serial sections he observed patchy fibrosis of the myocardium, with the bundle of His and the left bundle branch normal but with the right bundle branch interrupted at two points by fibrous lesions.

Hill[62] (1930) studied 2 cases of left bundle branch block histologically. In 1 case, however, he lost the right bundle branch 3 mm. below its origin and observed no lesions in the conduction system except a few small round cells in that branch. In the other case he lost the right branch in its upper half, but he said he thought it divided into two branches before he lost it, one branch passing deeply into the myocardium. He did not find lesions in the conduction system, but there was diffuse myocardial fibrosis.

In 1930 Oppenheimer and Oppenheimer[149] reported in abstract form their histologic data in 10 cases of intraventricular block, "including bundle-branch block and arborization block." The third and tenth cases were the cases previously reported by Oppenheimer and Pardee.[7] There were 5 cases of bundle branch block, 2 being cases of typical bundle branch block of the common discordant type and 3 being cases in which the electrocardiogram approached this type but was not per-

145. Wenckebach and Winterberg,[88] p. 349.

146. Marvin, H. M.: Paroxysmal Ventricular Tachycardia with Alternating Complexes Due to Digitalis Intoxication, Am. Heart J. **4**:21, 1928.

147. Taussig, H. B.: A Case of Bundle-Branch Block Confirmed by Pathological Study, Bull. Johns Hopkins Hosp. **45**:40, 1929.

148. Agostoni, G.: Un cas de lésion de la branche droite du faisceau de His, soupçonnée cliniquement, diagnostiquée par l'electrocardiogramme et controlée à l'autopsie, Arch. d. mal. du cœur **22**:577, 1929.

149. Oppenheimer, B., and Oppenheimer, E.: The Site of the Cardiac Lesion in Ten Cases of Interventricular Block Including Bundle-Branch Block and Aborization Block, Tr. A. Am. Physicians **45**:427, 1930.

fectly characteristic. In all 5 cases the histologic lesion was on the left side, and the right branch was intact except for a partial lesion in 1 case. Four other cases were instances of so-called arborization block. In all 4 the lesion involved the left bundle branch, "while the right branch was found to be intact throughout its course." The remaining case was one of "well-marked intraventricular block of the exceptional discordant type, in which the main ventricular deflection was directed downward in lead 1 and upward in lead 3 . . . The lesion in this case was found solely in the right bundle branch, the left branch being normal throughout its course." These results unequivocally support the new concept of bundle branch block. Surprisingly, however, in all but 1 case the opposite bundle branch was intact. Furthermore, these authors did not publish clinical histories, electrocardiograms, necropsy reports, descriptions of the histologic studies or photomicrographs in connection with any of the cases.

In 1931 Mahaim's [26] splendid volume on the organic diseases of the conduction system was published. Mahaim's thorough study of 8 cases of bundle branch block (7 right and 1 left, according to the original terminology) supported the original terminology, but in every case the lesions, mainly fibrosis due to vascular disease, were present in both bundle branches, although they were more nearly completely interruptive in the branch assumed, on the basis of the electrocardiogram, to be blocked. Electrocardiographically these were all cases of so-called intraventricular block, but in most of them there were differences from the original clinical criteria of bundle branch block, mainly in regard to amplitude, spread of the QRS complex and notching. In 2 cases the amplitude was small, the electrocardiograms resembling those of so-called arborization block. One case (observation XI) was an instance of complete heart block, with ventricular tachycardia and right bundle branch block. In cases 5, 6, 8, 9 and 10 there was a deep S deflection in lead I. The only important point open to doubt in Mahaim's study was the interpretation of the branch more severely affected, since serious lesions were present in both branches in all cases. Mahaim stressed the importance of studying the branches by serial sections as far down as they can be recognized, since in some of the cases he observed the important lesion in the lowermost part of the right branch. He made a strong point of the blood supply of the bundle branches, emphasizing the common source of supply of the right branch and the anterior division of the left, explaining thus the bilaterality of lesions and the escape of the posterior division of the left branch in many cases. Although Mahaim's work further beclouds the problems involved, it is of great value because it provides a careful review of the literature, it points out the necessity of thorough histologic study of the conduction system,

it emphasizes the usual bilaterality of lesions and their frequent vascular pathogenesis and it gives the author's thought-provoking deliberations.

In 1935 Mahaim,[150] reporting a study of 2 cases of right bundle branch block, reviewed his previous cases and eliminated all but 2 of his 7 cases as being indecisive. He excluded observation V because of the short period of clinical observation (two and a half months), an elongated PR interval and lesions of the common trunk. Observation VI was questioned because of the short period of clinical control (three weeks). Observation IX was discarded because of the short period of clinical study, the wide QRS complex and the multiple and bilateral lesions and because only one tracing had been made. Observation X was eliminated for the same reasons plus the presence of auricular fibrillation. Observation XI was excluded for similar reasons, "total bilateral lesions rendering the case problematical." Finally, he discarded observation XII because there was only a single tracing and because of the extended bilateral lesions without complete interruption of the left bundle branch, which he said he believed the electrocardiogram indicated. His criteria for determining which bundle branch influences the form of the electrocardiogram in bundle branch block had become much stricter. He said he considered as essential (1) prolonged clinical observation, with numerous electrocardiograms, (2) a constant, easily measurable and not prolonged PR interval, (3) the absence of tachycardia, auricular fibrillation, disturbances of auriculoventricular conduction and notably (4) the existence of no more than a slight prolongation of the QRS complex, since increases of over 0.1 second are due to extensive lesions of both bundle branches. If the anatomic lesions are clearcut, one does not need to be so rigorous about the clinical features, such as the length of the period of clinical control. He pointed out that the lesions of the bundle branches are almost always bilateral, which is the greatest source of error of interpretation, and that one cannot always be sure of the conductivity of a few fibers which might appear intact in a severely diseased branch. He stressed the point that if 1 of 10 sections shows definite lesions, one should stain and study some of the intervening sections also.

His new cases were interesting. Observation I concerned a man of 31 who had severe rheumatic lesions of the aortic and mitral valves and some tricuspid valvulitis. He had been followed eleven years. At first there was a normal electrocardiogram, then auricular fibrillation with slight right axis deviation and during the last six years auricular

150. Mahaim, I.: Nouvelles recherches sur les lésions du faisceau de His-Tawara; le bloc de branche gauche et sa pathogénie; la septite mitrale, Ann. de. méd. **38**:185, 1935.

fibrillation and right bundle branch block, with QRS never longer than 0.1 second; the T wave was almost iso-electric. In a thorough histologic study he observed severe generalized fibrotic lesions of the left branch from its origin. The bundle of His and the right bundle branch were only slightly affected. There was extensive scarring of the interventricular septum and of the endocardium of the left ventricle. Observation II concerned a man of 38 who had been observed for six months. There had existed during this time an irreducible auricular flutter with two to one block except during paroxysms of one to one rhythm brought about by effort. The heart rate was usually 120 per minute but at times 240. There was right bundle branch block, with a QRS interval of 0.11 second. Severe mitral stenosis and tricuspid valvulitis were observed at necropsy, with dilatation of the pulmonary artery and functional pulmonary insufficiency; the foramen ovale was widely patent. Complete interruption of the left bundle branch at its origin was noted, but there were also extensive fibrous and inflammatory lesions of the right branch due to "septitis of mitral origin." There were also serious hemorrhagic lesions of the right branch of recent origin.

In this same article Mahaim also pointed out that one must look carefully for a large offshoot of the posterior part of the uppermost portion of the left bundle branch. This branch, originally described by him,[151] in 1932, under the title "Le bloc bilatéral manqué," is supposed to arise high up near the bifurcation of the bundle of His and to pass directly into the septal myocardium, so that even complete lesions of the left bundle branch a little lower would not produce bundle branch block. In the patient in whom he discovered this offshoot there was active and healed septal myocarditis, with complete and extensive destruction of the left bundle branch and complete interruption also of the right bundle branch, but idioventricular rhythm did not result. Instead, there were a PR interval of 0.16 second, a QRS complex of 0.14 second, with low voltage and multiple notching, and a small slightly diphasic T wave. The main ventricular complex was upright in lead I but triphasic in lead III. The curves resembled those of "arborization block," and Mahaim concluded that such curves can be due to complete lesions of both bundle branches. He said he believed that the newly discovered connections can explain all discrepancies among the observations of various investigators and the various degrees of enlargement of QRS. The more extensive the lesion of the left bundle branch, the wider the QRS complex should be, since the excitation wave passing into the septal myocardium through the high offshoot would have a

151. Mahaim, I.: Nouvelles recherches sur les lésions du faisceau de His-Tawara; le bloc bilatéral manqué, nouvelle forme anatomique de bloc du cœur à substituer au bloc dit "d'arborisations," Ann. de. méd. **32**:347, 1932.

longer course to follow in the more slowly conducting myocardium until it reached healthy elements of the Purkinje system much farther down.

Meessen[152] (1935), studying the fetal calf heart, was unable to find connections through the interventricular septum between the two bundle branches or their network, as had been demonstrated by Cardwell and Abramson[153] (1931) and Wahlin[154] (1932). In 2 human hearts he could not verify the special superior and posterior connections of the left branch with the septum, as described by Mahaim in 1, but in the other he found many fine connections from the left branch to the septum. In 1 case the curves were typical of "arborization block" of the right bundle branch. Meessen found the conduction system intact down to the ramifications and conceived that the myocardium was cut off from the Purkinje network by fibrosis. In the other the curves were those of right bundle branch block, but there was myeloid infiltration of the left branch.

For the sake of completeness one should call attention to the work of Rosenthal[155] (1932), who studied the conduction system of 5 hearts histologically but did not give details of his technic or of his studies. In 1934 Géraudel,[156] who has made numerous but apparently incomplete microscopic studies, stated that there are no bundle branches or arborizations but that the main bundle crosses the fibrous septum and is lost immediately in the interventricular septum.

In 1936 Cornell, Claytor and I[112] reported 3 cases of auriculoventricular heart block due to bilateral bundle branch lesions, with detailed histologic studies of the conduction system. In the first case the electrocardiogram showed curves of essentially supraventricular type, and there were fibrotic lesions practically completely interrupting both bundle branches. In the second case the curves were typical of left bundle branch block; the upper half of the entire left bundle branch was almost completely replaced by dense fibrous tissue, and about one third of the cross-section of the right branch was replaced by fibrous tissue in the upper third of the branch. In the third case the curves showed complexes varying from that of right to that of left bundle

152. Meessen, H.: Zur normalen Histologie des Reizleitungssystems und zu seinen Störungen, Ztschr. f. Kreislaufforsch. **27**:42, 1935.

153. Cardwell, J. C., and Abramson, D. I.: The Atrioventricular Conduction System of the Beef Heart, Am. J. Anat. **49**:167, 1931.

154. Wahlin, B.: Die interventrikulären Verbindung im Reizleitungssystem des Herzens, Upsala läkaref. förh. **38**:1, 1932

155. Rosenthal, S. R.: Branch Arborization and Complete Heart Block, Arch. Int. Med. **50**:730 (Nov.) 1932.

156. Géraudel, E.: Le faisceau de His est un connecteur septo-septal; inexactitude du schéma de Tawara, Ann. d'anat. path. **11**:300, 1934.

branch block on different occasions; about 60 per cent of the track of the left bundle branch was replaced by fibrous tissue, and about 75 per cent of the cross-section of the right branch was likewise affected.

SUMMARIES OF SIXTEEN CASES OF BUNDLE BRANCH BLOCK STUDIED PATHOLOGICALLY

Before proceeding to a more detailed description of the 6 cases which constitute the main subject matter of this report, it would be of some value briefly to review the clinical records and gross morbid anatomic data for the 16 cases of bundle branch block that have been studied, as reports of pathologic studies of such cases are rare in the literature.

CASE 1 (previously reported as case 1 by Yater, Cornell and Claytor,[112] 1936).—A man aged 65 years had dyspnea on exertion and spells of dizziness, faintness and unconsciousness for more than a year before death. Complete heart block was known to have existed for three months before death, which occurred in an Adams-Stokes attack. Electrocardiograms showed left axis deviation and did not suggest bundle branch block, although the histologic lesions were confined to the bundle branches, the auriculoventricular node and bundle being uninvolved. The blood pressure was 160 systolic and 60 diastolic. The heart weighed 450 Gm. The myocardium appeared to be normal. The anterior descending coronary artery was sclerotic, and about 3 cm. from its origin it was constricted to about one quarter of its normal caliber. The other coronary arteries were somewhat thickened, but their lumens were of normal diameter. The endocardium and valves appeared normal. The pathogenesis of the bilateral bundle branch block was undoubtedly due to coronary arteriosclerosis.

CASE 2 (previously reported as case 2 by Yater, Cornell and Claytor,[112] 1936).—A man aged 63 years had had Adams-Stokes attacks for nearly four years. The blood pressure was 110 systolic and 60 diastolic. Electrocardiograms made at intervals during this period showed numerous changes in the ventricular complex. Before two to one heart block was established, the form was almost typically that of left bundle branch block. After two to one heart block had become established, the curves no longer typified bundle branch block. Finally, complete heart block supervened, with the reappearance of left bundle branch block. Death occurred during a prolonged convulsive seizure. The heart weighed 450 Gm. The large coronary arteries were not atheromatous or thickened, and their lumens were normal. The chambers were normal in size and not dilated. The myocardium showed no evidence of fibrosis grossly. The endocardium and valves appeared to be entirely normal. The cause of the histologic lesions of the conduction system, which consisted of fibrosis confined to the bundle branches (the left much more than the right), was coronary arteriosclerosis involving the small arteries in the interventricular septum, which were considerably thickened and narrowed in places.

CASE 3 (previously reported as case 3 by Yater, Cornell and Claytor,[112] 1936).—A man aged 49 years had some dyspnea on exertion and occasional dizzy spells for over a year before death. The blood pressure was 132 systolic and 88 diastolic. Thrombotic occlusion of the arteries of the right leg developed, and he died while under an anesthetic before amputation could be performed. Numerous electrocardiograms made during the last year of life showed varying degrees of auriculo-

ventricular heart block, with some periods of sinus rhythm. In all the electrocardiograms there was evidence of impaired conduction of one or the other bundle branch, more often of the left. The heart weighed 410 Gm. The large coronary arteries appeared normal, with an occasional small, slightly elevated atheromatous plaque. The myocardium was flabby and grayish red. In the posterior wall of the left ventricle near the apex and close to the septum there was a small scar, 0.8 cm. in diameter, with fine yellow mottling. There was also suggestion of scarring in the interventricular septum near the base anteriorly. The endocardium and valves were apparently normal. The pathogenesis of the incomplete but severe fibrosis of the two bundle branches was, again, probably due to disease of the coronary arteries. The small intramyocardial arteries were surrounded by much more than the normal amount of fibrous connective tissue.

CASE 4 (case 1 of the present report).—This was a case of right bundle branch block. The heart weighed 400 Gm. There was healed mitral valvulitis, without much stenosis. The large and small coronary arteries were dilated and thin walled. There was complete destruction of the right bundle branch by a dense myocardial scar. A few small scars were present elsewhere.

CASE 5 (case 2 of the present report).—This was a case of right bundle branch block. The heart weighed 560 Gm. There was extreme mitral scarring, with stenosis. The aortic and tricuspid valves were slightly affected. The large coronary arteries were not very sclerotic. There was a large scar in the endocardium of the left upper half of the interventricular septum. The right bundle branch was completely replaced by fibrous tissue in part of its course; the left branch was compromised by endocardial fibrosis.

CASE 6 (case 3 of the present report).—This was a case of right bundle branch block, with paroxysms of various degrees of partial auriculoventricular block and asystole. The heart weighed 450 Gm. It was not dilated, but all the chambers were hypertrophied, especially the left auricle, right ventricle and interventricular septum. There was extensive thickening of the endocardium, especially over the upper half of the left side of the interventricular septum. The myocardium showed streaks of fibrosis, most marked in the septum. The coronary arteries and the valves were normal. Serial sections showed extreme fibrosis of the myocardium, partial destruction of the auriculoventricular bundle by fibrosis, complete replacement of the lower half of the right bundle branch by fibrous tissue, almost complete destruction of the left bundle branch and sclerosis of the media of the small coronary arteries.

CASE 7 (case 4 of the present report).—This was a case of "incomplete" left bundle branch block. The heart weighed 460 Gm. The left ventricle was hypertrophied. The coronary arteries were thin and dilated. The valves were normal. The myocardium was practically normal. Serial sections showed the right bundle branch to be moderately fibrotic, and the left branch showed extensive interstitial fibrosis.

CASE 8 (case 5 of the present report).—This was a case of "incomplete" left bundle branch block. The heart weighed 550 Gm. and was dilated. There was severe coronary arteriosclerosis, with complete thrombotic occlusion of the anterior interventricular artery. There was an old healed infarct of the lower half of the interventricular septum and of the apical region of the left ventricle. The valves were normal. Serial sections showed moderate fibrosis of the midportion of the right bundle branch and severe compression of the left branch by fibrous tissue, with complete disappearance of the anterior division in the region of the infarct.

CASE 9 (case 6 of the present report).—This was a case of left bundle branch block. The heart weighed 575 Gm. and was greatly dilated. There was not much coronary arteriosclerosis. The myocardium did not appear abnormal. The valves were normal. Serial sections showed small discrete scars in the myocardium. The auriculoventricular node and bundle were moderately fibrotic. There were moderate fibrosis of the first portion of the right bundle branch and moderate and variable interstitial fibrosis of the left branch.

CASE 10 (Army Medical Museum accession no. 38706).—A man aged 43 years had been known to have a cardiac disorder for a year before death, with weakness, dyspnea on exertion and later progressive edema with orthopnea. The blood pressure was 106 systolic and 88 diastolic. An electrocardiogram showed left bundle branch block, without increase in amplitude of the ventricular complex. The heart weighed 490 Gm. and was dilated. The anterior descending coronary artery was calcified, with great reduction in the size of the lumen and a recent red thrombus. The left circumflex artery was similar, but the right coronary artery, although sclerotic, had a good lumen. A large infarct involved the apex of the left ventricle, and the interventricular septum was thinned and scarred. The latter was covered by a much thickened endocardium. A mural thrombus filled the apex of the left ventricle. The valves appeared normal. A histopathologic study of the conduction system has not been made.

CASE 11 (Army Medical Museum accession no. 40539).—A man aged 55 years began to have palpitation of the heart five years before he died and was told he had a large heart. For two years before death he had attacks of congestive heart failure. The heart was found to be large, and there was evidence of aortic regurgitation. The blood pressure was 164 systolic and 100 diastolic. Eight electrocardiograms made at intervals during the last eight months showed left bundle branch block, with little variation. The heart weighed 770 Gm. and was dilated. The hypertrophied myocardium was streaked with fibrous tissue. The aortic valve was thickened, with rolled free edges, and the anterior cusps were fused by a mass of calcium at the commissure. There was also extensive calcification at the line of attachment of the posterior cusp. The other valves were essentially normal. There was severe coronary arteriosclerosis, especially of the anterior interventricular artery, which was nearly occluded by the sclerosis. Serial sections were made of the conduction system but were not satisfactory.

CASE 12 (Army Medical Museum accession no. 40621).—A man aged 42 years had a cardiac attack suggestive of thrombosis of the coronary arteries two months before he died, which was the first indication of heart disease. The highest blood pressure was 145 systolic and 95 diastolic. Anginal attacks followed. Death occurred unexpectedly. An electrocardiogram showed "incomplete" left bundle branch block. The heart weighed 600 Gm. The anterior descending coronary artery was calcified and had a small lumen, which was filled with a recent thrombus. The right coronary artery was sclerotic but not occluded. There was a large healing infarct of the lower anterior wall and apical region of the left ventricle, and this area was covered by a large, flat mural thrombus. The valves appeared normal. A histopathologic study of the conduction system has not been made.

CASE 13 (Army Medical Museum accession no. 41621).—A man aged 62 years began to have attacks of dyspnea and precordial pain three months before he died. There was evidence of pulmonary congestion. The blood pressure was 95 systolic and 70 diastolic. Five electrocardiograms were made and were similar, showing left bundle branch block without increased amplitude. The heart weighed 670 Gm., but the much thickened adherent pericardium probably accounted for 150 Gm.

The heart was considerably dilated. The coronary arteries were all sclerotic and more or less completely calcified. Each of the anterior and posterior interventricular arteries was occluded by the sclerosis in its distal half. There was a large partially healed infarct involving the lower and anterior half of the interventricular septum. This area was thin and bulged into the right ventricle; it was covered on the left ventricular surface by a friable grayish red lamellated thrombus. The apical region and the lower portion of the anterior wall of the left ventricle were involved in the infarction. The valves were essentially normal except for some atheromatosis of the aortic cusps and of the aortic leaflet of the mitral valve. Serial sections were made of the conduction system but were not satisfactory.

Case 14 (Army Medical Museum accession no. 42974).—A Negro aged 48 years had been dyspneic for six months and had had a cough with expectoration of blood. Paroxysmal nocturnal dyspnea had developed. The blood pressure was 150 systolic and 130 diastolic. An electrocardiogram showed left bundle branch block, with low amplitude in lead I. The heart weighed 155 Gm. There were scars in the interventricular septum, at the bases of the papillary muscles and in the apical region of the left ventricle. The anterior descending artery showed moderate sclerosis but not much diminution in the caliber of the lumen; the other coronary arteries were only mildly sclerotic. Serial sections of the conduction system were made but were not satisfactory.

Case 15 (Army Medical Museum accession no. 43235).—A man aged 79 years had had some dyspnea for seven years, and an electrocardiogram showed impaired auriculoventricular conduction at the beginning of that time. For about a year two years before death the heart rate varied a great deal but was often slow, being often as low as 28. An electrocardiogram made two years before death showed two to one heart block, a QRS interval of 0.14 second, a large R wave and a large notched S wave in the three conventional leads and an upright T wave in these leads. An electrocardiogram made a year before death showed complete heart block, the same QRS complex in lead I, a small notched R wave and a large notched S wave in lead II, no R wave but a deep slurred S wave in lead III, a large upright T wave in all three leads, occasional coupling of ventricular complexes and frequent ventricular extrasystoles. An electrocardiogram made a month before death showed sinus rhythm, with a PR interval of 0.22 second and typical left bundle branch block, with a QRS interval of 0.14 second. Death resulted from heart failure. The heart weighed 650 Gm. There was hypertrophy of both ventricles, especially the left. There was moderate sclerosis of the coronary arteries but no appreciable reduction in the caliber of their lumens. The aortic valve was calcified, and the right and left anterior cusps were fused. A spur of calcium extended downward a short distance from the right side of the calcified posterior cusp into the left ventricle in the interventricular septum. The other valves were essentially normal. There was no gross scarring of the myocardium. Serial sections of the conduction system were made but were not satisfactory.

Case 16 (previously reported by Yater and Shapiro [157]).—A woman aged 21 years had been told she had heart disease at the age of 7 years. There was a long harsh systolic murmur which was loudest at the left sternal border. Electrocardiograms showed left axis deviation, a variable direction of the T wave in

157. Yater, W. M., and Shapiro, M. J.: Congenital Displacement of the Tricuspid Valve (Ebstein's Disease): Review and Report of a Case with Electrocardiographic Abnormalities and Detailed Histologic Study of the Conduction System, Ann. Int. Med. **11**:1043, 1937.

lead I and a QRS interval of 0.16 second. Death occurred unexpectedly during the night. The heart weighed 275 Gm. and was typical of Ebstein's disease or congenital displacement of the tricuspid valve down into the right ventricle. The right side of the heart was greatly enlarged but not hypertrophied. Serial sections of the conduction system did not show lesions, but the course of the right bundle branch was somewhat anomalous.

ANATOMY OF THE CONDUCTION SYSTEM

The anatomic and histologic structure of the conduction system has been well described by Keith, His, Tawara, de Witt and others. The sino-auricular node (Keith-Flack), or pace-maker, is not of concern here. However, briefly, it is a relatively long flat bundle of small thin compact interlacing fibers in a groundwork of connective tissue, situated subepicardially just below the mouth of the superior vena cava, with its longitudinal axis in the sulcus terminalis. Its cross-section is fusiform or roughly triangular, and a comparatively large artery runs down the middle. There are also a number of arterioles in its substance; nerves and nerve ganglions are present subepicardially in its vicinity, and often nerves are seen at its edge. Rarely a nerve cell is seen in the substance of the node. The fibers of the node resemble myocardial fibers but are much smaller; they show cross-striations in good sections.

The auriculoventricular node (Tawara) lies close to the right side of the posterior portion of the central fibrous body, that is, in the right auricle a short distance anterior to the orifice of the coronary sinus and just above the attachment of the medial or septal cusp of the tricuspid valve. A relatively large artery with branches usually runs through it. This node resembles the sino-auricular node in structure but is not so compact and contains somewhat less connective tissue. Its fibers are slightly thicker, and their cross-striations are more frequently visible. They are arranged in whorls. At the beginning of the node, that is, in its most posterior portion, its fibers are looser at the periphery and merge with the auricular myocardium. In older persons there is often considerable fatty connective tissue adjacent to the node on its superficial surfaces.

After a short distance, roughly 0.5 cm., the node invades the central fibrous body and becomes the auriculoventricular bundle (Kent, His), without any definite line of demarcation. The bundle runs obliquely downward in the lower part of the central fibrous body to the lower edge of the membranous portion of the interventricular septum, being often separated by some fibrous tissue in its anterior part from the myocardium of the septum. It has no true sheath but is contained largely within the central fibrous body, which protects it. The fibers of the bundle are larger than those of the auriculoventricular node and

run in parallel bundles. They resemble more the ventricular fibers but do not contain so much myoplasm. The connective tissue framework is delicate, and there is no main artery but a number of arterioles and venules. Sometimes in older persons there is a fair amount of adipose connective tissue in the bundle.

The auriculoventricular bundle runs for about 1 to 1.2 cm. and divides into right and left branches. The right branch appears to be more a continuation of the bundle and passes downward beneath the juncture of the medial and anterior leaflets of the tricuspid valve as a whitish threadlike process, at first being beneath the endocardium and not always distinctly separated from the surrounding cardiac muscle. A short distance down, about 0.5 cm., the branch comes to lie more deeply in the myocardium, where it runs in a cleft of connective tissue. After a variable distance, roughly 1 cm., it gradually works its way out along a cleft in the myocardium to the subendocardium again. Here it continues for about another 1 cm., spreading out to become a thin sheath of Purkinje fibers near the base of the anterior papillary muscle of the right ventricle, beyond which point it can rarely be recognized microscopically in the human heart. In its course it passes downward and anteriorly in the middle of the trabeculum of the ventricle, which corresponds to the moderator band of the beef heart. The fibers of the right branch are about the same size or a little larger than those of the myocardium, but they are usually paler. They are parallel and close together, and they often closely resemble the myocardial fibers. On cross-section the branch is variable in shape, being fusiform, oval, round or triangular in different portions.

The left bundle branch spreads out from the auriculoventricular bundle on the left side of the interventricular septum, at first as a thin layer of fibers. It is subendocardial throughout most of its course and becomes much thicker as it descends in the septum. It also gradually spreads out like a fan beneath the endocardium, and in the lower half of the septum it often divides into anterior and posterior divisions, one passing to the region of the base of the anterior papillary muscle and the other to the base of the posterior papillary muscle. In this region the Purkinje fibers rapidly spread out subendocardially among the usually numerous trabeculae and are no longer definitely recognizable. The endocardium is usually thicker in the upper part of the septum and contains discrete groups of smooth muscle fibers, which should not be mistaken for Purkinje fibers. Normally there is only a small amount of loose areolar connective tissue separating the bundle branch from the endocardium superficially and the myocardium deeply. The appearance of the fibers of the left branch in horizontal sections depends on the size of the heart and the degree of dilatation, as well

as on the portion of the septum being examined. These fibers are larger and much paler than myocardial fibers, containing a much less dense myoplasm. The myofibrils are more peripheral and more prominent; the cross-striations are usually readily observed but not as distinctly as in the myocardium. The Purkinje fibers become larger as the branch descends. Offshoots from the branch into the myocardium are practically never recognized in the human heart.

The vascularization of the conduction system has been capably studied, notably by Haas [158] (1911), Tandler [159] (1913), Gross [160] (1921), Mouchet [161] (1922), Crainicianu [162] (1922) and Spalteholz [163] (1924). The auriculoventricular node and bundle are supplied with blood almost entirely by one special artery, the ramus septi fibrosi, or the first posterior perforating artery, which passes forward into the auriculoventricular septum from the origin of the posterior descending, or interventricular, artery just at the point posteriorly where the two auricles and two ventricles meet. In approximately 90 per cent of hearts this is a branch of the right coronary artery, from the posterior extremity of its left circumflex branch, this artery then passing downward as the posterior descending artery. The anterior descending, or interventricular, artery may give a minor portion of the blood supply of the auriculoventricular bundle, especially in its anterior portion. As a rule the origin of the bundle branches also takes its main vascularization from this ramus septi fibrosi, but there are numerous variations. The vascular supply of the bundle branches is less positively known than that of the auriculoventricular node and bundle, but there is a general more or less definite arrangement. The arteries arise from the anterior and posterior descending, or interventricular, arteries and perforate the interventricular septum, passing toward its middle, where they anastomose to a certain extent. The left bundle branch, being spread out over the subendocardial surface of the left side of the septum and divided usually into an anterior and a posterior division, or ramification, has its blood supply both from the perforating septal branches of the anterior and from those of the posterior descending artery. In a general way the anterior perforating arteries supply the anterior divi-

158. Haas, G.: Ueber die Gefässversorgung des Reizleitungssystems des Herzens, Anat. Hefte **43**:627, 1911.

159. Tandler, J.: Anatomie des Herzens, Jena, Gustav Fischer, 1913.

160. Gross, L.: The Blood Supply to the Heart, New York, Paul B. Hoeber, 1921.

161. Mouchet, A.: Les artères coronaires du cœur chez l'homme, Paris, Norbert Maloine, 1922.

162. Crainicianu, A.: Anatomische Studien über die Coronararterien und experimentelle Untersuchungen über ihre Durchgängigkeit, Virchows Arch. f. path. Anat. **238**:1, 1922.

163. Spalteholz, W.: Die Arterien der Herzwand, Leipzig, S. Hirzel. 1924.

sion of the left bundle branch, and the posterior perforating arteries supply the posterior division. The vascularization of the right bundle branch, a threadlike fasciculus, is not so definitely known but is most probably almost entirely derived from the perforating septal arteries of the anterior descending artery except, perhaps, in its terminal portion, which may receive some of its blood supply from the lower posterior perforating arteries. The upper third of the branch is probably supplied mainly by the two uppermost anterior perforating arteries and the middle third by a special branch of the second perforating artery, the ramus limbi dextri (Gross). This same special artery probably nourishes most of the lower third of the branch. The anastomoses between the anterior and the posterior perforating arteries are probably very fine and not particularly effective in cases of sudden obstruction, as has been shown so well by Crainicianu. In slow obliteration these anastomoses are probably more efficacious in maintaining an adequate blood supply than in sudden occlusion.

Thus it is seen that the blood supply of the auriculoventricular node and bundle and of the posterior division of the left bundle branch comes mainly from the perforating septal arteries of the posterior descending, or interventricular, artery (in 90 per cent of the cases a branch of the right coronary artery), whereas the blood supply of the right bundle branch and of the anterior division of the left branch is almost entirely derived from the perforating septal branches of the anterior descending, or interventricular, artery.

HISTOLOGIC TECHNIC

A full time expert technician can properly prepare on the average 4 to 6 hearts per year for study of the conduction system. Unfortunately, at least 1 of these hearts must usually be discarded because of technical flaws due mainly to the difficulties of making thousands of uniformly good sections of a heart.

It is best not to keep a heart more than a few months, and the solution of formaldehyde employed should not be allowed to become more concentrated than a 1:10 dilution of the U. S. P. (40 per cent) solution. After the blocks of tissue have been embedded in paraffin, soaking them in water for from one to three weeks improves the quality of the cardiac muscle for sectioning. There is no specific stain for the conduction system, since the fibers are structurally very similar to those of the myocardium. In a fresh heart there may be more glycogen in the Purkinje fibers, but the use of some stain for glycogen, such as Best's carmine dye, is impracticable for routine work or extensive studies. Masson's trichrome stain gives the best coloring effects for study. The myocardium and conduction tissue are red, and connective tissue is green. In photomicrographs the parenchyma is dark, and the fibrous tissue is light, with a light red filter. Van Gieson's picrofuchsin stain is also good, but it fades after a time. This stains the parenchyma yellow and the connective tissue red, and in photomicrographs the parenchyma is light and the connective tissue dark.

The use of a dissecting microscope is invaluable for orientation and for studying so many sections, although a regular microscope must also be used frequently. The use of a dictaphone is time-saving when sections are being described.

It is vital to follow the bundle branches from beginning to end by means of serial sections, since one may not be able to identify them otherwise when they are the seat of lesions. This is especially true of the right branch, which is so small in diameter and so similar histologically to the myocardium that often it may not be definitely recognized in isolated sections, especially in its intramyocardial portion. It can be traced from below upward as well as from above downward, since in its lower subendocardial portion it is as easy to identify as it is from its origin in the bundle of His. However, lesions of the right branch are easier of interpretation than those of the left branch for the very reason that the right branch is so slender and readily studied in individual sections. When the left branch is diseased it sometimes happens that the isolated Purkinje fibers are difficult to distinguish from the fibers of the myocardium subjacent to the endocardium. This is especially true in the lower third of the interventricular septum, where the left branch is spreading out and dividing into smaller groups of Purkinje fibers. Purkinje fibers in the substance of the myocardium of the human heart are impossible to recognize but undoubtedly exist, just as they do in the hearts of large animals. There is considerable variation in the anatomic features of the left branch, the division into two portions about the middle of the septum, the anterior and the posterior, being often indefinite.

It is well not to make too many blocks from the septum but to make the blocks as large as possible and to include the whole thickness of the septum. Technicians complain but can usually make the sections satisfactorily if they are efficient. The branches are much more easily followed with fewer blocks. Usually 3 or 4 blocks can be cut to include the entire microscopically recognizable portion of the conduction system.

REPORT OF SIX CASES OF BUNDLE BRANCH BLOCK, WITH DETAILED HISTOPATHOLOGIC STUDY OF THE CONDUCTION SYSTEM

CASE 1[164] (Army Medical Museum accession no. 46390).—*Clinical Record.*—The patient was 50 years old at the time of his death on Feb. 26, 1935. From his thirteenth year on he had lived a roving, dissipated life, changing occupations frequently, but apparently always making a "good living." In the course of his many occupations he had been a soldier, farmer and lineman. Until 1924 he had been in good health. Then he began to have dyspnea and lack of endurance. His blood pressure was first recorded in 1932, when it was 130 systolic and 82 diastolic. From that time there had been a steady increase in the blood pressure to 186 systolic and 136 diastolic shortly before death. He was first hospitalized with symptoms of cardiac embarrassment on Nov. 6, 1934, and two days later the first electrocardiogram showed the presence of "incomplete" right bundle branch block. The heart was enlarged to the left as far as the anterior axillary line. A loud blowing systolic murmur was heard over the entire precordium but was loudest at the apex. The second heart sound at the apex was slightly reduplicated intermittently. Occasional premature beats were noted. There were three subsequent hospitalizations, all because of cardiac distress, which was more pronounced each

164. Major John G. Knauer gave me permission to use the records of this case and to study the heart.

time. Enlargement of the liver was not detected until January 1935. Edema of the lower extremities was present only once, two weeks before death, although orthopnea and marked hepatic congestion had been present for three weeks. Evidence of edema of the bases of the lungs was noted only in November 1934; otherwise edema was inconspicuous, and little was observed at necropsy.

The entire illness was essentially due to chronic heart failure, although the actual terminal event was acute perforation of the duodenum at the site of an old peptic ulcer, with resulting general peritonitis. A diagnosis of quiescent duodenal ulcer was made in March 1932, but symptoms referable thereto were almost negligible until the afternoon prior to the day of death.

The electrocardiograms recorded on Nov. 6 and 27, 1934, and on Jan. 22, 1935, were in general similar. The QRS complex measured 0.125 second and showed a deep S wave in lead I and an upright initial ventricular complex in lead III, with marked broadening and slurring or notching in all three conventional leads. The

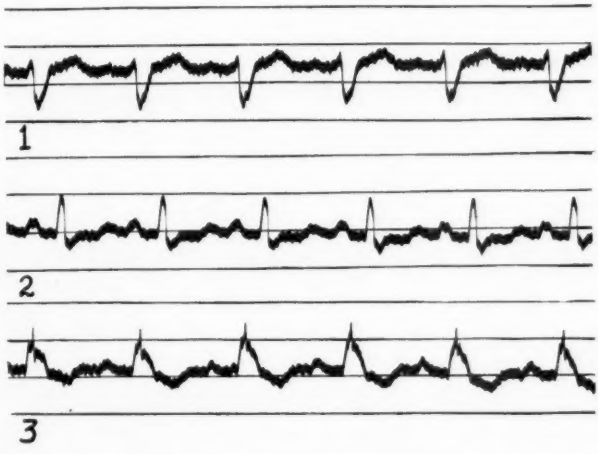

Fig. 1 (case 1).—Right bundle branch block. The QRS interval was 0.125 second.

T waves were not directed oppositely to all the main ventricular complexes, however, except in the last record (fig. 1). The PR interval was 0.162 second. The electrocardiogram made on Nov. 27, 1934, showed also an interpolated extrasystole preceded by the P wave and a shortened PR interval; the main initial ventricular complex was upright in lead I and down in lead III, with the T wave directed oppositely. The QRS complex was broad and slurred. A solitary QRS complex in lead I was of normal width and form and was preceded by a normal P wave with the same PR interval as in the majority of the QRS complexes; it was followed by an inverted T wave, in contradistinction to the QRS complexes elsewhere in the record, which were followed by positive T waves.

Necropsy (performed by Dr. Earl R. Lundeberg).—Necropsy was performed on the embalmed body the third day after death. The following anatomic diagnoses were recorded after a thorough examination: acutely perforated duodenal

ulcer; generalized peritonitis; severe cloudy swelling of the kidneys; acute septic lymphadenitis of the abdominal nodes; follicular hyperplasia of the spleen; fibrosis and cloudy swelling of the liver; cardiac hypertrophy (heart unopened at the time); congestion of the lungs, liver and kidneys; moderate atherosclerosis of the aorta, with moderate dilatation; calcification of the iliac arteries; cholelithiasis; chronic fibrous cholecystitis; slight apical pulmonary emphysema; a calcified tubercle in the right lung; simple cysts of the kidneys; an accessory spleen; bilateral arcus senilis; slight senile atrophy of the cerebral cortex; multiple ulcerations of the skin, and emaciation.

Gross Examination of the Heart: The heart weighed 400 Gm. There was no pericarditis. The left auricle was moderately dilated but not hypertrophied. The mitral valve showed a moderate degree of healed valvulitis, mainly at its free edge and especially on the aortic leaflet, which was considerably thickened at its edge and had one definitely thickened and other slightly thickened chordae tendineae. There was little stenosis, the effect of the lesion having been mainly regurgitation. The left ventricle was slightly hypertrophied. The aortic valve was apparently normal, and the root of the aorta was only moderately atheromatous. The right auricle was moderately dilated. The tricuspid valve was apparently normal. The right ventricle was moderately hypertrophied and dilated. The pulmonary valve appeared normal. The endocardium and myocardium throughout appeared normal. The coronary arteries were considerably dilated throughout and only moderately atheromatous.

Histopathologic Examination of the Heart: Four blocks were removed from the auriculoventricular and interventricular septums, which included practically all the microscopically recognizable portion of the conduction system. Block 1 included the entire thickness of these septums and contained the auriculoventricular node and bundle and the origins of the bundle branches. Serial sections were made vertically from behind forward so that the conduction system could be followed progressively from its origin. Block 2 included a long section of the right side of the interventricular septum and contained most of the right bundle branch. Blocks 3 and 4 included between them all the left side of the interventricular septum and therefore most of the left bundle branch. Blocks 2, 3 and 4 were cut serially from above down in the horizontal plane. All blocks were embedded in paraffin, and the serial sections were 10 microns thick. All sections were mounted and kept, but only every tenth one was stained, except in certain areas where others were also stained. Masson's trichrome stain was used mainly. Block 1 was cut into 2,490 sections, block 2 into 2,480 sections and block 3 into 1,500 sections. Only part of block 4 was cut, since it stained poorly.

The auricular myocardium was moderately fibrotic; the blood vessels throughout were greatly dilated, as they were elsewhere in the heart. The arteries showed little sclerosis. The auriculoventricular node was fibrosed in its first portion to the extent of about 50 per cent by an increase in interstitial connective tissue. As it reached its greatest diameter, this fibrosis decreased, and the node became almost normal. The artery to the node was large and dilated and had several branches. Because of the dilatation the course of the arteries was easily followed. Adjacent to the central fibrous body, nearer its left side, there was a large area of fatty replacement of the auricular myocardium. The bundle of His was moderately fibrotic in its inferior half. Toward its end it became even more fibrosed, being replaced about 50 per cent by fibrous tissue. The endocardium on the left side of the interventricular septum was somewhat thickened. The left bundle branch in its upper part contained dense fibrous tissue among its fibers.

but these were apparently not badly damaged. Subjacent to the branch in its upper part there was replacement of the peripheral portion of the myocardium by dense fibrous tissue. As far down as the left bundle branch was traced it contained more than the normal amount of interstitial connective tissue. The bundle of His continued as usual into the right bundle branch. The first portion of this branch was densely fibrosed. In its beginning it was cut longitudinally and was

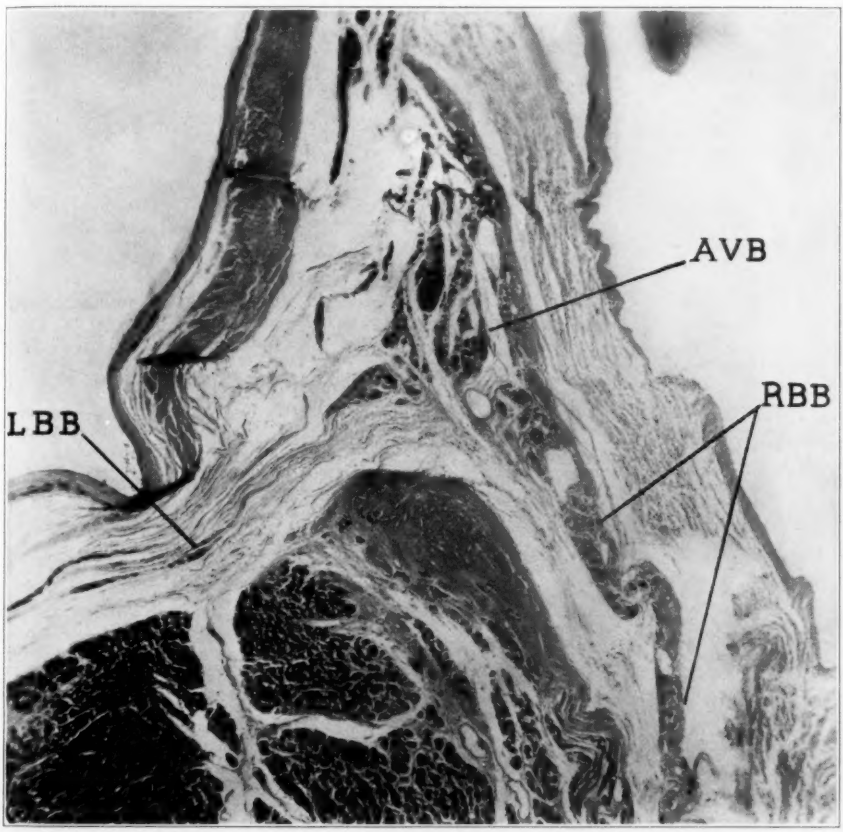

Fig. 2 (case 1).—Section 1,580, block 1, showing in vertical cross-section the moderately fibrotic auriculoventricular bundle (*AVB*), the moderately fibrotic left bundle branch (*LBB*) and the densely fibrotic right bundle branch (*RBB*); × 75.

mainly a mass of hyaline fibrous tissue, with a few conduction fibers embedded therein (fig. 2). The peripheral portion of the myocardium subjacent to the right bundle branch was almost entirely replaced by dense fibrous tissue. As the branch descended in its first few millimeters this area of myocardial fibrosis widened out into a solid scar, several millimeters in diameter, in which the right

bundle branch became embedded and completely lost its identity (fig. 3). Large irregular endothelium-lined spaces were present in the peripheral portions of the scar. After having vanished in the scar for about 3 mm. of its myocardial portion (the middle portion of the branch), the right bundle branch was seen gradually emerging from the lower peripheral portion of the scar (fig. 4). The branch

Fig. 3 (case 1).—Section 470, block 2, showing the dense, solid scar in the interventricular septum in which the right bundle branch has become completely destroyed; × 117.

gradually assumed a more nearly normal appearance and gradually approached the slightly thickened endocardium, where it spread out in its usual way. Throughout this part of its course it contained a little more than the normal amount of interstitial connective tissue. The upper half of the interventricular septum, par-

ticularly the myocardium, in general, contained a little more than the normal amount of connective tissue between the muscle fibers. Most of the muscle fibers were somewhat shriveled, owing probably to long fixation in solution of formaldehyde. There were also a few small scars in the myocardium besides the

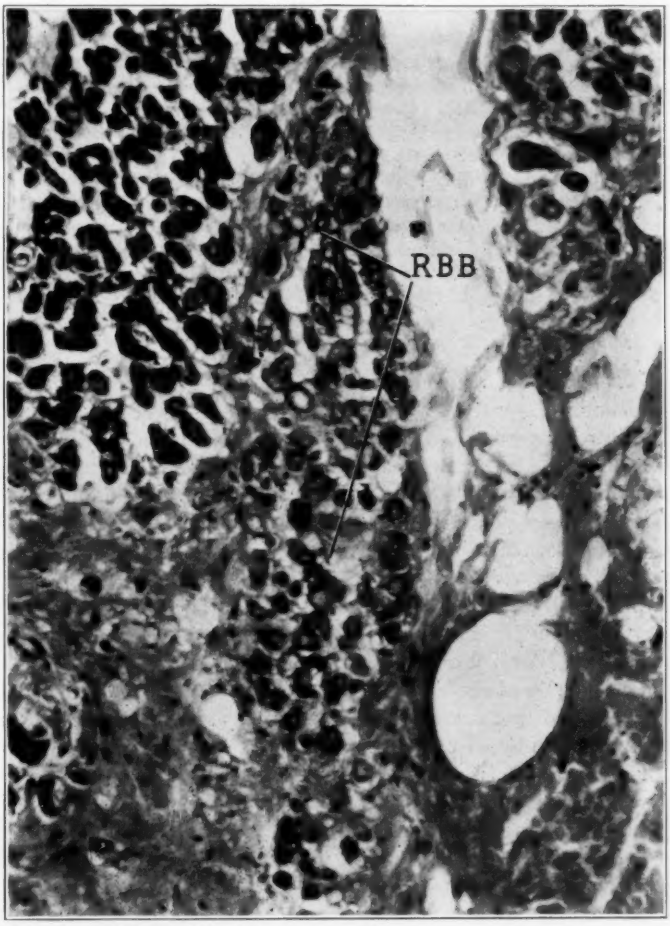

Fig. 4 (case 1).—Section 850, block 2, showing in cross-section the right bundle branch (*RBB*) gradually emerging from the lower peripheral portion of the scar shown in figure 3; × 263.

main one already described. The vessels throughout were dilated and thin walled, and endothelium-lined blood spaces of various sizes and shapes were numerous. In a few areas there was discrete diapedesis of erythrocytes. Many

of the arteries, especially the larger ones, were surrounded by more than the normal amount of connective tissue. The capillaries and arterioles in the bundle branches were often intensely engorged. The tricuspid valve as it appeared in the sections was essentially normal.

Summary.—A man aged 50 years presented evidence of heart disease for more than a year before his death, but the etiologic factor thereof was not clear. Shortly before death occurred the liver became engorged, but there was little edema detectable otherwise. Electrocardiograms showed "right bundle branch block," which was not complete, however, until just before death. General peritonitis, the result of acute perforation of a chronic duodenal ulcer, hastened death. The heart was moderately enlarged. The mitral valve showed healed valvulitis which had produced regurgitation but not much stenosis. The coronary arteries were all dilated and thin walled. Serial sections of the conduction system showed some fibrosis of the auriculoventricular node and bundle. The left bundle branch contained definitely more than the normal amount of interstitial connective tissue throughout. The first portion of the right bundle branch was very fibrotic, and in a short part of its intramyocardial course it was completely destroyed by involvement in a dense peripheral myocardial scar. The remainder of the branch was relatively normal. The myocardium in general was somewhat fibrotic and contained a few small definite scars.

Comment.—The pathogenic factor in this case was probably ancient rheumatic arteritis which produced myocardial infarction in the region of the intramyocardial portion of the right bundle branch and destroyed a portion of it. The vascular disease had resulted in thinning and dilatation of the vessels. The only other plausible explanation would be that the myocardial changes resulted from rheumatic myocarditis, but the character of the lesions was much more suggestive of healed infarcts. The small scars were not large enough greatly to compromise the function of the myocardium. The arterial disease, however, had produced malnutrition of the left bundle branch and of the endocardium, with resulting moderate but extensive interstitial fibrosis of the branch. The fibrotic condition of the bundle of His was not severe enough to produce impairment of auriculoventricular conduction. The bundle branch block was certainly of many years' standing, since the lesions all indicated great age, but there was no history of the time of onset of the rheumatic infection. The electrocardiogram did not show the large voltage originally described for bundle branch block, but it fulfilled the original criteria in other respects. Speculation would be interesting but inconclusive in regard to the cause of the single QRS complex of normal form referred to.

CASE 2[165] (Army Medical Museum accession no. 50187).—*Clinical Record.*—Mrs. E. M., a housewife aged 46 years, was admitted to the Torbett Sanatorium and Diagnostic Clinic, Marlin, Texas, on March 26, 1936, complaining of shortness of breath, flutter and palpitation of the heart, pain in the chest and swelling of the

165. Dr. J. Walter Torbett Jr., of the Torbett Sanatorium, gave me permission to use the records of this case and to study the heart.

feet and legs. She had typhoid in childhood and many typical attacks of inflammatory rheumatism between the ages of 8 and 33 years. She had an operation for gallstones fifteen years before entry. Dyspnea on exertion and precordial pain had first been noted nine years before entry, but she had not consulted a physician. These symptoms did not become severe until four years before entry, when more dyspnea, wheezing and rattling noises in the chest and a sense of oppression or dull aching in the chest and neck developed. She attributed these symptoms to obesity, attempted to reduce and went to bed for a while, still without consulting a physician. Attacks of "asthma" lasting three to four weeks then began to occur about twice a year. She improved somewhat, but one and a half years before she was admitted to the hospital her heart began to "flutter and skip and beat fast," and there was considerable pain in the chest. A physician then told her that she had an enlarged heart, with leakage and irregular action. Six months before admission to the hospital she began to have orthopnea, with severe coughing at the onset, and two months before entry, edema appeared in the feet and gradually ascended to the waist. Recently she had coughed up frothy pink material. She had not taken any medicine for her heart.

Physical examination revealed an obese orthopneic woman, with cyanosis of the ears, fingers, toes and lips. The veins of the neck were greatly distended. The arterioles of the retinas showed moderate tortuosity and some arteriovenous compression, and the margins of the optic disks were slightly blurred. There were impaired resonance, with some diminution of intensity of the breath sounds, and moist rales at the bases of the lungs. The apex beat was diffuse, and the exact size of the heart could not be determined. The heart sounds were muffled and distant. The cardiac rhythm was totally irregular, and the rate was about 100 per minute. A distant to and fro murmur heard over the apex and along the left sternal border was thought to be that of mitral stenosis. The radial pulse was almost imperceptible. The blood pressure was determined with difficulty and was about 110 systolic and 40 diastolic. There was marked pitting edema of the lower extremities, the abdomen and the back. The edge of the liver could not be felt because of the obesity and edema. The temperature was normal. The urine contained albumin, grade 2. A hemogram and the blood urea were normal. Wassermann and Kahn tests of the blood gave a negative reaction.

Electrocardiograms showed typical right bundle branch block, auricular fibrillation and an occasional ventricular extrasystole (fig. 5). The rate varied from 110 to 120 per minute according to the number of premature beats. The amplitude was not appreciably increased. The QRS interval was 0.12 second. Definite notching was present in lead II. There was slight variation in the configuration of the complexes. Electrocardiograms on two consecutive days showed the T wave broader and rounder and the heart rate considerably slower on the second day.

The patient was given the usual treatment for congestive failure, although there were some diuresis and slowing of the heart rate to 70 per minute. She died on April 2, seven days after admission to the hospital.

Necropsy.—Permission for necropsy included only study of the chest. The heart was removed three hours after death and placed in solution of formaldehyde U. S. P. diluted 1 : 10.

Gross Examination of the Heart: The heart weighed 560 Gm. The two layers of the pericardium were almost completely adherent because of old fibrous adhesions. The large coronary arteries were relatively little affected by any degenerative process. The aorta showed practically no atherosclerosis. The left auricle was hypertrophied and dilated, grade 2. There were two smooth, fibrous plaques, about 1.5 cm. in diameter, in the endocardium of the posterior wall. The

mitral valve was densely fibrotic and largely calcified, and there was stenosis, grade 4, of the auriculoventricular orifice. The chordae tendineae were moderately thickened and greatly shortened. The cavity of the left ventricle was relatively small. The wall was 2.3 cm. thick in its upper third. The aortic valve was moderately fibrotic, and its two anterior cusps were fused. There had evidently been a little stenosis and regurgitation. The membranous portion of the interventricular septum was thickened and fibrotic. In the left ventricle just below the junction of the membranous and muscular portions of the septum there was a circular fibrous plaque, about 1 cm. in diameter, directly in the track of the first part of the left bundle branch (fig. 6). It had a thick, elevated, rounded rim and a depressed center. The remainder of the endocardium of the left ventricle appeared normal except for an area below the plaque, where it was a little thickened and white. There were some small patches of white fibrous tissue in the myocardium and some thin fibrous linear areas. The right auricle was hypertrophied and dilated like the left. The tricuspid valve showed fibrous

Fig. 5 (case 2).—Auricular fibrillation and right bundle branch block, with a QRS interval of 0.12 second and a ventricular premature contraction.

scarring, with fusion between the septal and the anterior leaflet, but the function of the valve apparently had not been much altered. The valve at the area of scarring was considerably thickened just at the point where the right bundle branch arises, and for some distance below that the endocardium was apparently thickened. The right ventricle was not much dilated. Its wall was 0.75 cm. thick in its upper third. The pulmonary valve appeared normal, and the pulmonary artery was smooth.

Histopathologic Examination of the Heart: Three blocks were removed from the heart which included the lower part of the auriculoventricular septum and the major portion of the interventricular septum. All 3 included the entire thickness of the septums. Blocks 1 and 2 contained the greater portion of the conduction system. Block 1 contained the auriculoventricular node and bundle and the origins of the bundle branches. Serial sections were made vertically from behind forward so that the conduction system could be followed progressively from its origin. Block 2 included the upper two thirds of the interventricular septum and contained the major portion of the two bundle branches. This block was cut serially from

above down in the horizontal plane. Block 3 was embedded in paraffin but was not cut, since the important lesions were found to be in block 2 and only a small portion of the two branches remained in block 3. Blocks 1 and 2 were embedded in paraffin, and the serial sections were 10 microns thick. All sections were mounted, but only every tenth one was stained. Masson's trichrome stain was used. All sections were numbered and kept permanently. Block 1 was cut into 2,080 sections and block 2 into 1,820 sections.

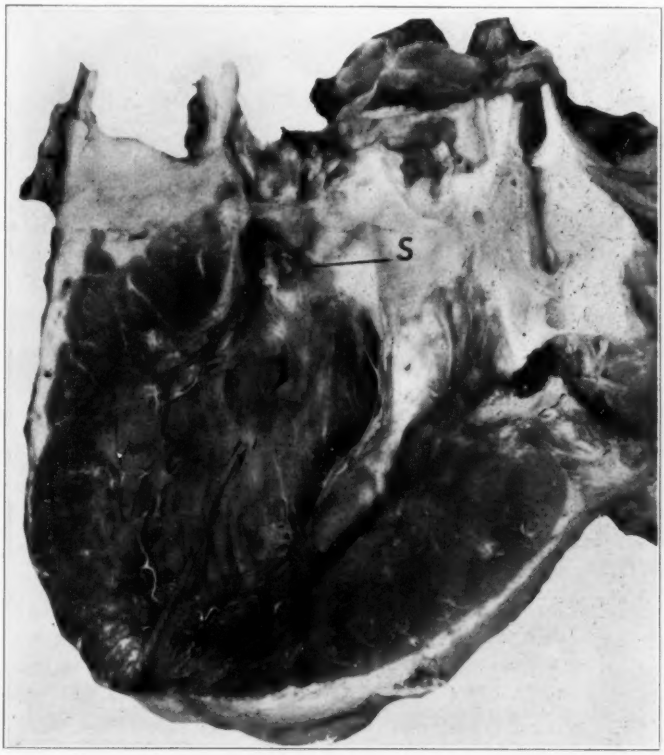

Fig. 6 (case 2).—The opened left ventricle, showing the left side of the interventricular septum with the circular fibrous plaque (*S*) just below the aortic valve in the track of the first part of the left bundle branch.

The auricular myocardium in block 1 was considerably degenerated. There was a moderate increase in the amount of interstitial fibrous connective tissue, and many of the myocardial fibers showed degeneration mainly in the nature of edema, giving a vacuolated appearance. The myofibrils were distinctly separated and no longer parallel. Many of the fibers appeared to be no more than empty tubes with a thin membranous wall. The cross-striations were indistinct and

granular. In some areas the auricular myocardium presented a fibrotic, gnarled appearance. The exocardium was greatly thickened owing to fibrosis. The myocardium of the upper portion of the interventricular septum contained in this block was moderately fibrotic. There was not as much degeneration of the myocardial fibers as in some parts of block 2.

Fig. 7 (case 2).—An arteriole of the interventricular septum, showing subintimal proliferation, scarring of the media and a thrombus in the lumen attached to the intima by thin strands of fibrin; × 289.

Practically all the arteries and arterioles throughout all the sections showed definite evidence of healed rheumatic arteritis. In many instances these changes affected all the coats of the vessels. One of the commonest changes, especially in the smaller vessels, was subintimal fibroblastic proliferation and edema (fig. 7). The media was also often edematous and contained pale collagenous tissue, with

the muscle fibers reduced in number, separated and often arranged in patches (fig. 8). The walls of the arteries, especially of the larger ones, were irregularly thickened, and the lumens were irregularly narrowed. Sometimes one side of the wall was thin and the other thick and markedly degenerated. An occasional arteriole was completely occluded by fibroblasts (fig. 8*C*). The adventitia and surrounding fascia often contained an excess of fibrous tissue. Many of the smaller arteries and arterioles contained relatively fresh thrombi in the center of their lumens, with thin strands of fibrin passing between the intima and the thrombus. The vessels seemed to be present in increased numbers, especially about the periphery of and within the central fibrous body. The vessels within the elements of the conduction system were affected similarly to those elsewhere, but the capillaries were often more distended, giving the appearance of intense congestion.

The auriculoventricular node was degenerated in much the same way as the auricular myocardium and contained somewhat more than the normal amount of connective tissue. Both the auriculoventricular node and the first half of the bundle contained some relatively large empty spaces, possibly dilated lymph channels. The bundle of His appeared to be more nearly normal than the node and contained only a slight excess of connective tissue. The fibers were cut transversely, as they are in the technic employed, and the myofibrils stood out prominently, giving a granular appearance to the fibers. The first portion of the left bundle branch seen, the upper posterior part, was relatively normal, lying under a slightly thickened endocardium. As the raised endocardial scar on the left side of the septum was approached, the branch passed down under its base and was embedded in fibrous tissue (fig. 9). It became thinner, and its fibers were often more separated. The fibers varied in size, many being broader than normal and presenting a vacuolated appearance. The branch seemed to have considerable difficulty in passing beneath the middle and anterior portions of the scar, being thin, but nowhere was it completely interrupted. The raised endocardial scar was thick and was composed of dense fibrous tissue, with a sprinkling of nuclei. In its base there were large irregular endothelium-lined spaces containing blood. The root and proximal portion of the septal leaflet of the tricuspid valve was thick, fibrous and vascular. Toward its end the bundle of His contained a little more fibrous tissue than in its main extent. It terminated in the usual way as the right bundle branch. The first part of this branch appeared fairly normal, but as it approached the endocardium it became progressively fibrotic, until about half of it was replaced by fibrous tissue. Beyond this point in block 1 the amount of fibrous tissue slowly decreased to about 25 per cent of the substance of the branch, but the branch was passing into an area of severe fibrosis beneath the endocardium near the base of the tricuspid valve. The mitral and aortic valves were thick, fibrous and vascular.

In block 2 the bundle branches were cut transversely. The first portion of the right bundle branch seen was fairly normal, but it rapidly became fibrotic as it lay just beneath the attachment of a markedly fibrotic chorda tendineae which had its roots in a dense scar in the myocardium. This bundle branch finally became so replaced by hyaline fibrous tissue that only one or two thin muscle fibers remained embedded in the scar (fig. 10). One or two small blood vessels remained in it. This situation maintained for some little distance (from section 260 to section 460), but then the fibrosis gradually decreased until in the third, or lower, subendocardial portion of the branch it consisted of only about 10 per cent of fibrous tissue between the muscle fibers. It was no longer embedded in the myocardial scar. The left bundle branch continued downward uninterruptedly in the

Fig. 8 (case 2).—Three arterioles in the interventricular septum, showing in *A* one with a very fibrous and distorted media; in *B* one with marked edema of the media and a narrowed lumen, and in *C* one completely occluded by fibroblasts; × 361.

subendocardial areolar tissue of the left side of the septum, but it was not normal. Its fibers were variable in diameter; the larger ones looked like vacuoles, and there was considerable fibrous tissue among the fibers. The lower part of the raised endocardial scar was present for some distance, beneath which the branch was most affected (fig. 11). The branch spread out beneath the otherwise fairly normal endocardium as usual, but a definite division into anterior and posterior divisions was not apparent (as is not infrequently the case in the human heart). The branch was followed into the bases of the papillary muscles, mainly, however, the anterior, where the fibers were large, close together, pale and almost normal.

Fig. 9 (case 2).—Section 1,060, block 1 (× 133), showing the upper portion of the left bundle branch (*LBB*) passing between the myocardium and the endocardial scar (*S*) pictured in figure 6. An arteriole is shown (at *A*) similar to the one pictured in figure 7.

The passage into the base of the posterior papillary muscle was not so easy to follow, because the fibers were smaller and more separated. The myocardium of the interventricular septum in block 2 was considerably degenerated in many areas. Except for the scar in the region of the middle portion of the right bundle branch, there was only a moderate increase in interstitial connective tissue, but there were many foci in which there was considerable edema of the myocardium and what appeared much like liquefaction necrosis.

Summary.—A woman, aged 46 years at the time of death, had had frequent attacks of rheumatic fever since the age of 8 years. For nine years she had had symptoms suggestive of heart disease, and for more than six months there had been symptoms of severe congestive failure. Electrocardiograms made a few days

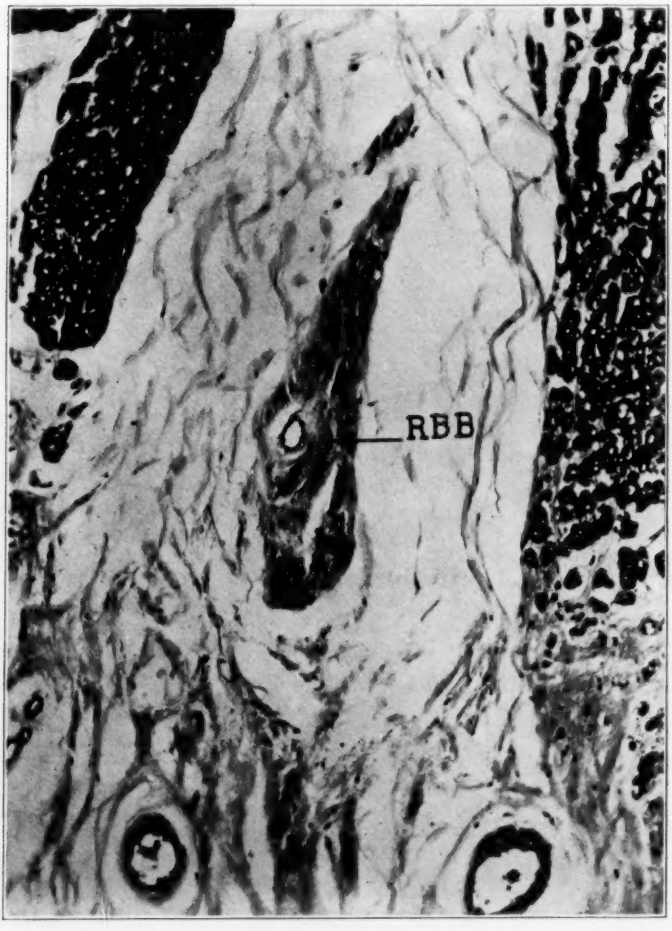

Fig. 10 (case 2).—Section 260, block 2, showing in cross-section the right bundle branch (*RBB*) almost completely replaced by hyaline fibrous tissue; × 137.

before death showed right bundle branch block, auricular fibrillation and extrasystoles. The heart showed severe mitral stenosis and moderate scarring of the aortic and tricuspid valves. There was a raised endocardial scar in the upper part of the left side of the interventricular septum. The myocardium showed micro-

scopically patchy degeneration and healed rheumatic arteritis. Serial sections through the conduction system showed that the auriculoventricular node and bundle were only slightly degenerated, but there was practically complete replacement of the right bundle branch by hyaline fibrous tissue in part of its intramyocardial portion as it entered a scar in the peripheral part of the myocardium. The left bundle branch was not normal, particularly as it passed beneath the raised endocardial scar, but it was not interrupted in any portion. Many of its fibers were swollen and embedded loosely in fibrous connective tissue.

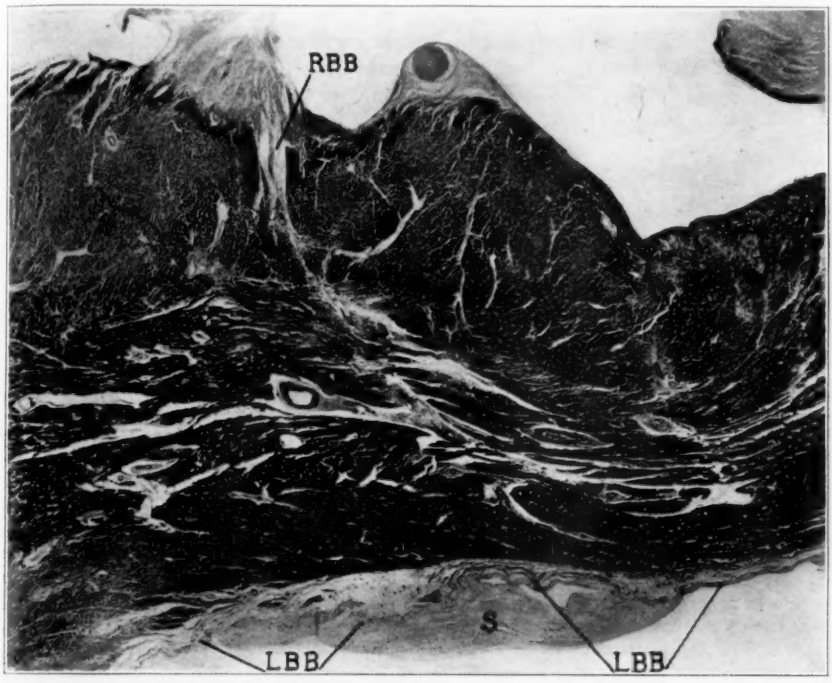

Fig. 11 (case 2).—Section 220, block 2, showing the interventricular septum in cross-section, with the fibrotic right bundle branch (*RBB*) near the right side (top) and the compromised left bundle branch on the left side (bottom); × 10.

Comment.—The pathogenesis of the myocardial degeneration and the main lesions of the bundle branches was undoubtedly due to old rheumatic arteritis, although the endocardial scar in the left ventricle which comprised the left branch was probably due to endocarditis. The arterial disease was extensive and affected only the small arteries and arterioles. Similar vascular lesions due to rheumatic infection have

been described by Karsner and Bayless [166] (1934); by Gross, Kugel and Epstein [167] (1935), and by others. There was no doubt as to the bundle branch more seriously affected. It is unbelievable that the right branch could conduct at all.

The case illustrates well the point that it is impossible usually from a gross examination of the heart to state which bundle branch is destroyed. The endocardial scar lying in the track of the beginning of the left branch could readily have been considered adequate to cause destruction of that branch, but extensive histologic study showed the branch probably to be capable of functioning, whereas the right branch, unassociated with any indictable gross lesion, was almost totally destroyed in part of its course. As in case 1, the amplitude of the ventricular complex was not great.

CASE 3 [168] (Army Medical Museum accession no. 44641).—*Clinical Record.*—A young man, aged 24 years at the time of his death, on Nov. 1, 1934, had never been seriously ill until shortly before that time. He had never had rheumatic fever but had had some mild attacks of sore throat. Five years before his final illness he had a cough for a short time, and a cardiac murmur had been discovered and attributed to chronic tonsillitis. He had engaged in athletics without difficulty, but after this illness he abandoned strenuous sports, although he continued to work and study hard. In May 1934 he suddenly fainted but recovered quickly and felt as usual thereafter. On August 21, however, after a busy and exciting period of preparation for marriage, he awoke feeling bad and somewhat dyspneic on exertion. Examination at this time revealed a tall, slender young man who did not appear ill. The examination revealed no abnormality except moderate enlargement of the heart, the dulness extending about 10 cm. to the left of the midsternal line in the fifth intercostal space, and a loud high-pitched systolic precordial murmur. The pulse rate was 80 per minute and regular, and the blood pressure was 100 systolic and 70 diastolic. The patient was reassured, and he resumed his usual activities without further symptoms. On September 26 he had a second short fainting spell during a busy evening. On the following day he had several short attacks of syncope. His pulse was found to vary in rate and strength, being slow and strong during the attacks and more rapid and weak between them. The use of ephedrine had a beneficial effect.

The first electrocardiogram was made on this day (fig. 12). It showed sinus rhythm at the time, with a rate of 80 per minute. The PR interval measured 0.16 second and the QRS complex 0.16 second in all three leads. The main ventricular complex was down in lead I and upright in leads II and III. It was notched in lead I and severely slurred in leads II and III. In the latter leads the amplitude was 20 and 22 mm., respectively. The T wave was upright in lead I and deeply inverted in leads II and III, in which it passed almost directly downward from the descending limb of the R wave.

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166. Karsner, H. T., and Bayless, F.: Coronary Arteries in Rheumatic Fever, Am. Heart J. **9**:557, 1934.

167. Gross, L.; Kugel, M. A., and Epstein, E. Z.: Lesions of the Coronary Arteries and Their Branches in Rheumatic Fever, Am. J. Path. **11**:253, 1935.

168. Dr. Benjamin F. Weems had charge of the patient and gave me permission to study the heart and report the case.

From this time on the patient suffered almost daily from these brief attacks of syncope. It became apparent that there were varying degrees of heart block, with short periods of asystole, in which the patient became pale and unconscious. During these periods the auricular pulse could be observed in the veins of the neck. In some attacks there were as many as 125 auricular contractions without a single ventricular beat. Electrocardiograms made on October 2 verified these findings (fig. 13). The general characteristics of the complexes were the same as in the first tracing. The auricular rate throughout the periods of block was rapid, usually about 140 per minute, and it was more rapid the greater the degree of auriculoventricular block. During the phases of sinus rhythm the rate was about 80 per minute. The P wave was notched and tall during the periods of block, measuring as much as 5 mm. The PR interval varied with different periods

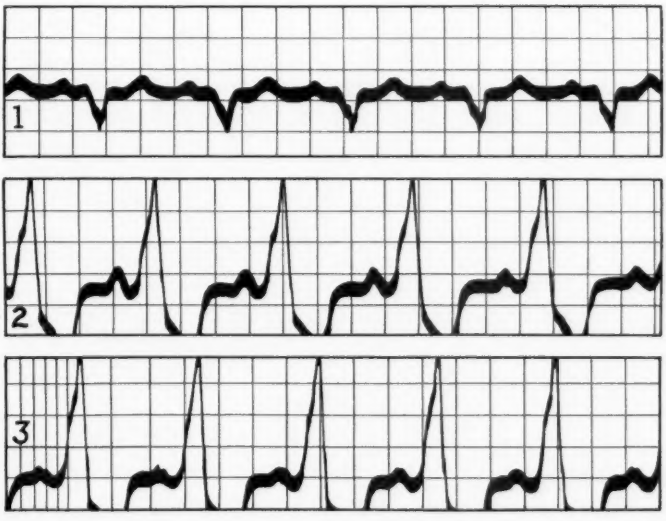

Fig. 12 (case 3).—Right bundle branch block with large amplitude in leads II and III and a QRS interval of 0.16 second.

of block. A striking point was the fact that neither in this nor in subsequent electrocardiograms were there any periods of idioventricular rhythm and that Wenckebach periods were never noted. The amplitude of the waves in leads II and III was greater than it was in the first tracing, the R wave being 38 mm. high. Electrocardiograms made on two subsequent occasions were similar.

During one attack of unconsciousness, on October 4, the patient became opisthotonic and ceased to breathe. Injections of solution of epinephrine apparently restored him. Nausea and vomiting developed and became very troublesome. Vomiting appeared to precipitate many of the attacks of unconsciousness. In spite of the frequent administration of ephedrine, the syncopal attacks continued to occur many times daily. Epinephrine was injected from time to time. Digitalization was attempted with the idea of producing permanent complete heart block and stabilizing the cardiac action, but vomiting precluded the oral administration of

the drug, and it was discontinued after a few doses. A few days later digifoline was given intravenously. The pulse rate became 32 per minute and remained at about this figure for many hours at a time, during which the syncopal attacks were much less frequent. The patient repeatedly complained of gastric and intestinal flatulence and paroxysms of pain of a crampy nature in the lower portion of the abdomen. The ephedrine used was held to be at least partly responsible for much of the gastro-intestinal disturbance, and the dosage was reduced. However, there was little amelioration, and the patient died in an Adams-Stokes attack during the night, less than six months after his first syncopal attack and a little more than

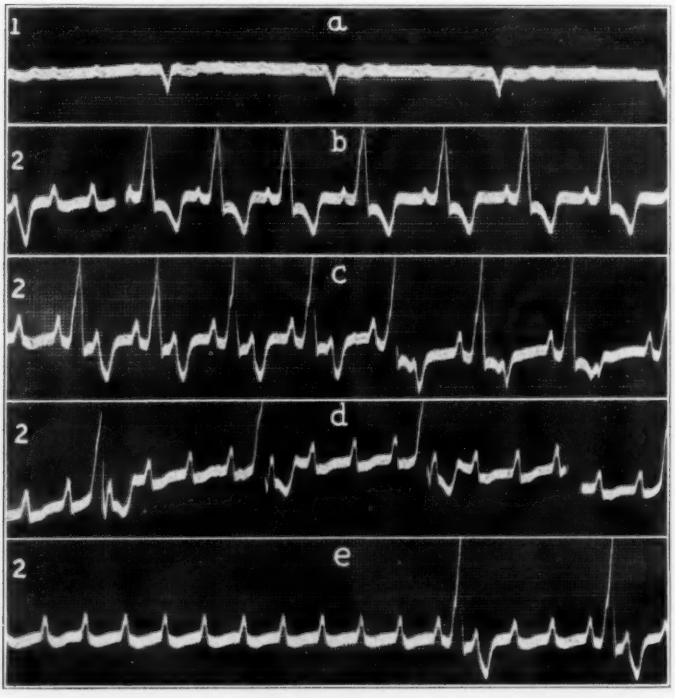

Fig. 13 (case 3).—Composite reproduction of sections of several electrocardiograms, all sections except the uppermost showing lead II. *a*, (lead I) there is four to one heart block; *b*, most of the tracing shows sinus rhythm; *c*, two to one heart block; *d*, four to one heart block; *e*, a long period of asystole (only partly shown) is followed by a period of four to one block. In *c*, *d* and *e* the P wave is tall and notched. The PR interval varies. A large amplitude is shown in all tracings of lead II.

a month after the attacks became frequent. At no time had there been any evidence of an active inflammatory process. The patient remained at home, and few laboratory tests were performed.

Necropsy.—Necropsy was performed by Dr. Weems less than three hours after the patient died. There was essentially no abnormality except for emaciation and old fibrous adhesions to the upper lobe of the left lung. There was no evidence of passive congestion.

Gross Examination of the Heart: The heart weighed 450 Gm. The pericardium had a generally milky tinge. On the lateral surface of the left ventricle near the base and apex and also near the base of the right ventricle posteriorly, there were a few subepicardial hemorrhages, about 0.5 cm. in diameter. The chambers were not dilated, but they were all hypertrophied, especially the left auricle and the right ventricle. The former was about 0.5 cm. and the latter 0.8 cm. thick. The average thickness of the left ventricle was 1.5 cm. The interventricular septum was very thick, about 3 cm., and grossly showed much scarring. All the valves

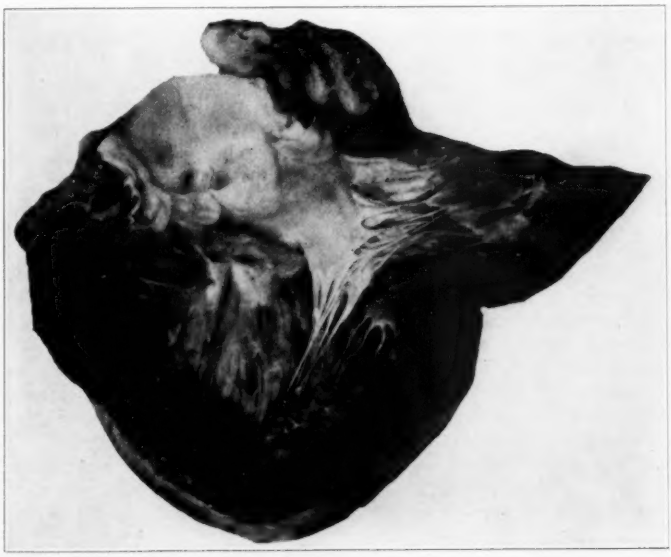

Fig. 14 (case 3).—The opened left ventricle, showing hypertrophy of this ventricle and whitish thickening of the interventricular septum, especially in the upper portion.

appeared normal. The measurements of the valvular orifices were as follows: aortic, 6 cm.; mitral, 8.5 cm.; pulmonic, 6.5 cm.; tricuspid, 9 cm. There were a few streaks of white in the myocardium in general. The endocardium of the left ventricle over the membranous portion and the upper part of the muscular portion of the interventricular septum for about 3 cm. below the aortic valve appeared thick and white (fig. 14). A similar appearance was noted on the ventricular endocardium beneath the anterior leaf of the mitral valve. Below these areas there was a less notable and more patchy milky appearance of the endocardium over the septum. On the right side of the septum the endocardium presented a moderately milky appearance, but nowhere was this as marked as on the left side. The endocardium of both auricles had a slightly milky appearance. The foramen

ovale was closed. The orifices of the coronary arteries and the vessels themselves appeared normal. There was slight atheroma of the root of the aorta.

Histopathologic Study of the Heart: Blocks of tissue were removed from the auriculoventricular and interventricular septums which included practically all the microscopically recognizable portion of the conduction system. Block 1 included the auriculoventricular node and bundle and the origin of the two bundle branches. Serial sections were cut vertically from behind forward after the block had been embedded in paraffin. This block was cut into 1,040 sections of 10 microns thickness; all were mounted, and every tenth section was stained with Masson's trichrome preparation. Block 2 included the greater part of the interventricular septum, which because of its thickness had been cut down the middle in such a way that this block contained the left half of the septum with the endocardium of the left ventricular surface and therefore most of the left bundle branch. There were 1,517 sections made from block 2, all of which were mounted, and every tenth section was stained with Masson's trichrome preparation. Block 3 contained the opposite half of the interventricular septum facing the right ventricle; it therefore contained the right bundle branch. The block was cut into 1,860 sections, many of which were stained with Van Gieson's connective tissue stain and many with Masson's stain, all being mounted. A total of 4,417 sections was made.

The artery of the auriculoventricular node was much thickened, as were many of the arteries in the myocardium (fig. 15). The thickening was due not to intimal changes but to fibrosis of the media particularly, so that this coat was fragmented and appeared moth eaten. The thickness of the wall was irregular. The lumen was moderately reduced in diameter. A rim of dense fibrous tissue surrounded many of the arteries. The node was only slightly abnormal, with a small increase in interstitial connective tissue. The auricular myocardium was moderately fibrotic. The auriculoventricular bundle was considerably more fibrotic than the node, about 20 to 25 per cent of its substance being dense interstitial connective tissue in its first half and close to 50 per cent being fibrous tissue in its other half, which lay just below the central fibrous body and nearer the left side of the septum than usual. The origin of the right bundle branch was at least 50 per cent fibrotic, whereas the origin of the left branch was perhaps less so.

The endocardium of the upper third of the left side of the interventricular septum was replaced by dense acellular fibrous tissue, which was 2 mm. thick in some parts. Below this it became rapidly thinner and finally of nearly normal thickness. In the upper third of the septum there were a few patches of dense scar tissue. These rapidly became larger and more numerous until the septum was composed almost entirely (at least 80 per cent) of scar tissue. There was no evidence of recent inflammatory reaction. The left bundle branch was represented by only a few fibers in the middle of the septum. These were deep in the thickened endocardium and close to the myocardium in the upper half but were more superficial lower down (fig. 16). In the lower half of the septum they were so few and so difficult to distinguish from the myocardial fibers isolated in the scar tissue that one could not be entirely sure there were any left.

The upper endocardial portion of the right bundle branch was only moderately replaced by fibrous tissue (fig. 17*A*), but as the branch penetrated into the myocardium adjacent to a small peripheral scar it rapidly became replaced by fibrous tissue and lost its identity (fig. 17 *B* to *D*). The scar tissue representing the branch could be followed, however, and this finally approached the endocardium, where it became a triangular area of loose connective tissue entirely devoid of Purkinje fibers. There was no question about the complete replacement of the right bundle branch in its lower half.

One section of the lateral wall of the left auricle showed moderate scarring, one from the base of the lateral wall of the left ventricle showed a great deal of fibrous tissue and one from the lateral wall of the right ventricle showed only a moderate amount of scar tissue.

Summary.—A man aged 24 years was told he had a cardiac murmur five years before he died. Less than six months before he died he had a short attack of

Fig. 15 (case 3).—A small artery of the interventricular septum, showing the moth-eaten appearance of the media due to fibrosis and edema, irregular thickening of the wall and moderate reduction in the size of the lumen; × 85.

syncope. A little more than a month before he died similar attacks recurred and became more and more frequent. Great variation in the pulse rate was noted, and the syncopal attacks occurred during periods of asystole. Electrocardiograms showed almost classic right bundle branch block and many transitions from sinus

rhythm to different degrees of partial heart block and asystole. They did not show any periods of idioventricular rhythm, however. Death occurred in an Adams-Stokes seizure. The heart was moderately enlarged; its chambers were hypertrophied, especially the left auricle and the right ventricle, but they were not dilated. The valves and large coronary arteries appeared normal. The endo-

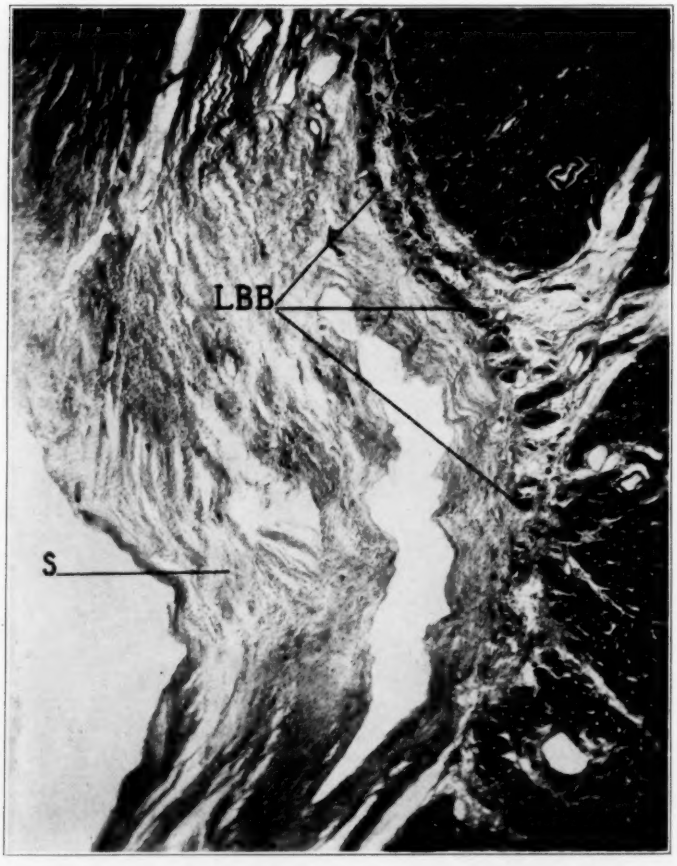

Fig. 16 (case 3).—Section 309, block 2, showing in horizontal cross-section the remnants of the left bundle branch (*LBB*) lying beneath the greatly thickened endocardium; × 54.

cardium of all the chambers showed patchy whitening, which was most marked on the left side of the interventricular septum. Histologic study showed diffuse and extreme fibrous scarring of the myocardium and thickening and fibrosis of the walls of the intramyocardial arteries, especially of the medial coat. The auriculoventricular node was slightly fibrotic, but the bundle of His was fibrotic to the

extent of about 50 per cent of its substance in its distal half. The left bundle branch was represented by a few fibers lying beneath the thickened fibrous endocardium; these almost disappeared in the lower half of the septum. The right bundle branch became progressively more fibrotic and was completely replaced by dense fibrous tissue in its distal half.

Comment.—The pathogenesis in this most remarkable case was not clear, but it seems probable that here again it was due to old rheumatic

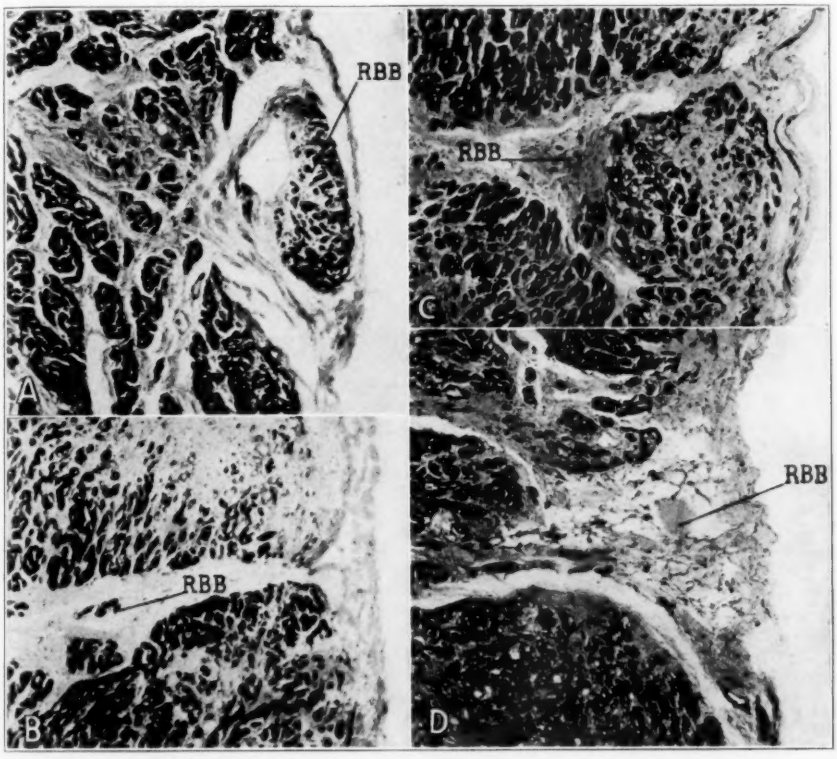

Fig. 17 (case 3).—*A*, section 135, block 3, showing in horizontal cross-section moderate fibrosis of the first portion of the right bundle branch (*RBB*). *B*, section 961, block 3, showing only a few fibers remaining in the intramyocardial portion of the right bundle branch, which is adjacent to a small myocardial scar. *C*, section 1,030, block 3, showing complete replacement of the intramyocardial portion of the right bundle branch by fibrous tissue. *D*, section 1,273, block 3, showing the right bundle branch still completely replaced by fibrous tissue in its third, or subendocardial, portion. Compare *D* with figure 20, which shows a relatively normal right branch in about the same region. All sections (× 25) show the fibrotic condition of the myocardium, which, however, is not as marked as at other points.

arteritis and endocarditis. There was definite widespread arterial disease of a kind not due to ordinary arteriosclerosis. The absence of valvulitis, however, threw some doubt on the assumption of a rheumatic etiology. The hypertrophy of the chambers most affected in mitral valvulitis, namely, the left auricle and the right ventricle, was extraordinary, in view of the absence of mitral disease. However, the left ventricle and the interventricular septum were also hypertrophied. The case suggests that disease of the coronary arteries and of the myocardium are capable of producing cardiac hypertrophy.

The extensive destruction of both bundle branches was astounding, but although it was almost unbelievable that the left bundle branch could conduct at all, which it did not do at times, there was no question as to the inability of the right branch to function.

CASE 4 (Army Medical Museum accession no. 48678).—*Clinical Record.*—The patient was a woman aged 65 years. She had apparently been in good health until a year before admission to the Georgetown University Hospital, on Jan. 5, 1936, three days before death. For a year she had had dyspnea on exertion and had received digitalis, the use of which for some reason had been discontinued. In September 1935 dyspnea reappeared, and she was digitalized and ordered to bed by another physician. She improved, but two weeks before her admission to the hospital the dyspnea increased. The day before entry she experienced a sudden "choking pain" over the upper sternal region which radiated around the neck. The pain increased, and when the physician saw her he noted "moderate signs of shock and orthopnea." The temperature was 98.6 F., the pulse rate 100 per minute and the blood pressure 185 systolic and 90 diastolic. The heart did not appear to be enlarged; there was a soft systolic apical murmur. Crepitant rales were heard at the bases of the lungs. An injection of morphine (0.03 Gm.) relieved the pain. During the day a pericardial friction rub was noted in the midsternal region, and the patient became cyanotic and more dyspneic. The systolic blood pressure fell only 6 mm. of mercury. The patient was admitted at 2:30 a. m., the diagnosis being acute coronary occlusion. She was stuporous, and the findings already noted were verified. The axillary temperature was 99 F., the pulse rate 90 per minute and the respiratory rate 12 per minute. In a few hours the blood pressure had fallen to 142 systolic and 60 diastolic.

An electrocardiogram showed a rate of 90, sinus rhythm, increased amplitude of the main ventricular complex and of the T wave, left axis deviation, a PR interval of 0.24 second, a QRS amplitude of 0.1 to 0.13 second and the T wave in a direction opposite to that of the main ventricular complex in the three conventional leads (fig. 18). The interpretation was "first degree auriculoventricular heart block, left axis deviation and intraventricular block of the left bundle branch type."

Urinalysis showed a specific gravity of 0.01, 4 plus albumin and a few leukocytes and erythrocytes. The hemoglobin value was 33 per cent; the erythrocytes numbered 1,960,000 per cubic millimeter of blood, with considerable poikilocytosis and anisocytosis, and the leukocytes numbered 10,000 per cubic millimeter of blood, with 85 per cent polymorphonuclear neutrophils. The nonprotein nitrogen content was 180 mg. per hundred cubic centimeters of blood.

An additional diagnosis of severe renal insufficiency was made.

The patient became comatose, and the cyanosis, orthopnea and pulmonary rales increased. The venous pressure was 205 mm. of saline solution (Griffith method). The temperature, after rising to 100 F. by axilla, dropped to 96.8 F.; and the pulse rate, after rising to 100, dropped to 70 per minute. The blood pressure dropped to 110 systolic and 54 diastolic just before death.

Necropsy.—Besides the heart, the viscera of interest were the kidneys, which were markedly contracted and granular (one weighing 55 Gm. and the other 90

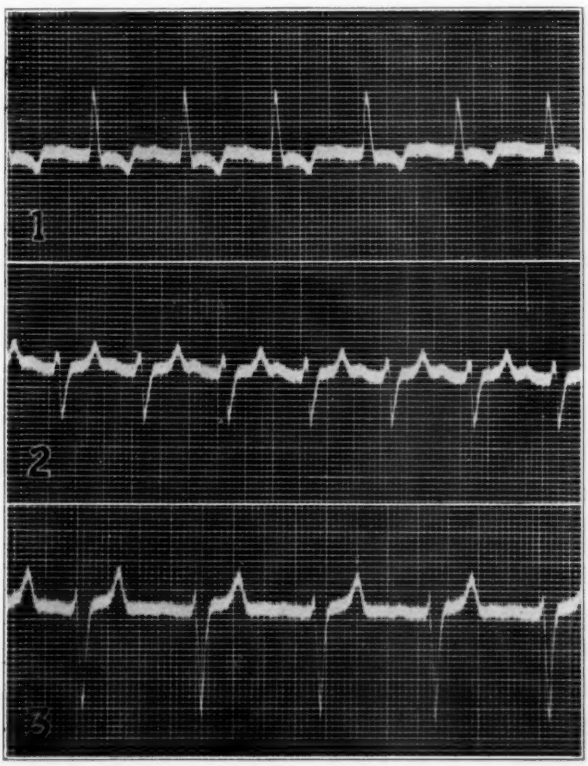

Fig. 18 (case 4).—Incomplete left bundle branch block, with QRS intervals of 0.1 to 0.13 second and a PR interval of 0.24 second.

Gm.) and the lungs, which presented edema of the lower lobes. Microscopically the kidneys were typical secondarily contracted organs.

Gross Examination of the Heart: The heart weighed 460 Gm. There was a thin deposit of fibrin on the epicardium. The left ventricle was moderately hypertrophied; its thickness was 1.5 cm. in the upper half. The right ventricle was 0.5 cm. thick in its upper half, and the interventricular septum was 1.7 cm. thick and wider than usual. The myocardium on section appeared normal. The

valves were all apparently normal, and the valvular orifices were of normal circumference. The coronary arteries were all patent and even a little larger in diameter than normal; they showed only moderate atherosclerotic change. The root of the aorta likewise presented only moderate atherosclerotic alteration.

Histopathologic Study of the Heart: Blocks were removed from the heart exactly as they were from the heart in case 2 and were prepared, cut, mounted and stained practically in the same manner. Block 1 was cut into 2,510 sections, block 2 into 1,590 sections, block 3 into 1,390 sections and block 4 into 1,530 sections, making a total of 7,020 sections. The auricular myocardium showed little increase in interstitial connective tissue, no more, in fact, than is usually seen in the hearts of most patients of this age. The ventricular myocardium throughout contained a slight excess of interstitial connective tissue also but probably no more than is usually seen in the hearts of most patients of this age. The intramyocardial arteries and arterioles in general appeared likewise to be no more degenerated than usual. Only one vessel was distinctly abnormal, namely, a septal artery running in the ventricular myocardium just beneath the central fibrous body. The wall of this vessel was thickened, and the lumen was reduced in diameter about 50 per cent. This artery gave off a relatively large branch, which passed downward and laterally to the left subendocardial region. One small artery in the auricular myocardium and another in the ventricular were also somewhat abnormal; they suggested superficially the rheumatic arteritis in case 1, with the media disorganized by fibrous tissue and the lumen decreased in diameter. However, it did not appear that there was sufficient vascular disease to be of any great significance.

The auriculoventricular node contained about the same slight degree of excess interstitial connective tissue as the myocardium in general. The greater portion of the auriculoventricular bundle was similar to the node, but as it continued on into the right bundle branch it was about 15 per cent fibrous tissue. The right bundle branch soon became definitely abnormal, in that it was about 40 per cent fibrous tissue, but most of this fibrous tissue was in the right half of the cross-section of the branch, where it had replaced the greater part of the conducting fibers (fig. 19). This fibrosis involved only about 3 mm. of the branch, after which it rapidly decreased, leaving the branch relatively normal throughout the remainder of its course (fig. 20).

The left bundle branch soon after its origin from the bundle of His showed distinct changes throughout its entire length and breadth. This branch was much more extensive than usual and was not distinctly separated into anterior and posterior divisions until it was low down in the septum. Some parts of it were thin; others were thick. The main abnormality consisted of an extensive but varying increase of interstitial connective tissue, which in some places was dense and separated the Purkinje fibers considerably (fig. 21), while in other regions in the same and in different planes it was thin and did not separate the muscle fibers much. This fibrosis was observed to be confined to the subendocardial region and did not involve the septal myocardium. The fibrous tissue was thicker on the endocardial side of the branch than on the myocardial side. Throughout its course, however, the fibers of the left bundle branch, even where embedded in the densest fibrous tissue, appeared fairly normal in structure. An interesting feature was the increase in thickness of the smooth muscle layer of the endocardium, which, however, varied considerably in different parts of the endocardium. Another interesting feature was the presence of an offshoot of Purkinje fibers from the left bundle branch at about the junction of the upper and middle thirds of the septum. This offshoot was as thick as the bundle branch and passed down

a short distance into a cleft in the myocardium (fig. 22). Although most of the sections of this region were stained, it did not appear that this offshoot went any great distance into the septum. This is the first time I have seen such a formation. The amount of fibrous tissue in the left bundle branch decreased

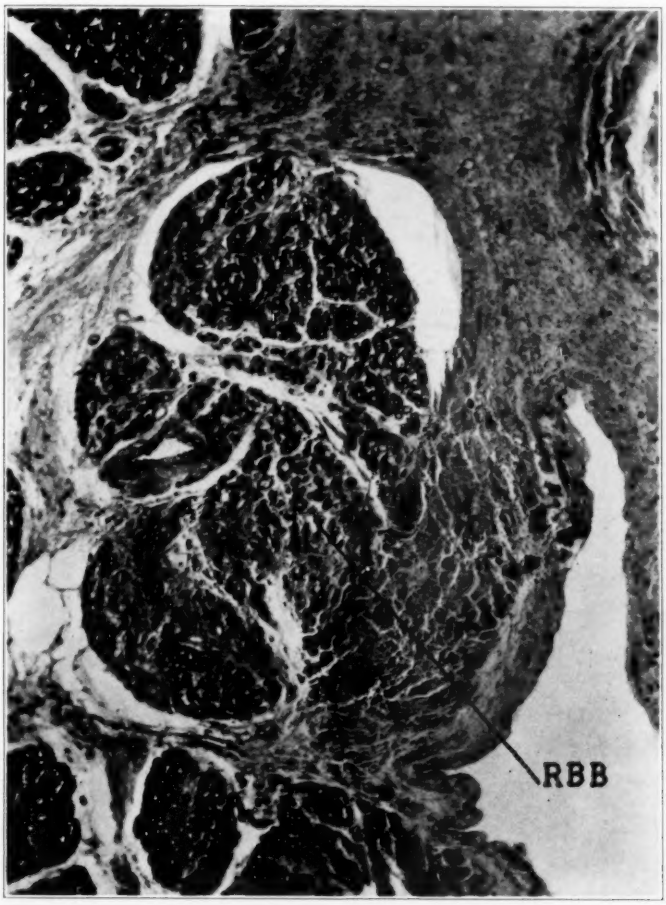

Fig. 19 (case 4).—Section 70, block 2, showing in horizontal cross-section moderate fibrosis of the right bundle branch in its first portion; × 92.

considerably in the lower region, where the elements of the branch passed over to the bases of the papillary muscles.

Summary.—A woman aged 65 years had had dyspnea for a year. A few days before death, severe pain developed in the upper portion of the sternum, and

she rather rapidly passed into coma. The blood pressure, which had been moderately elevated, dropped progressively. There were orthopnea, some cyanosis, rales in the bases of the lungs and a little fever. The nonprotein nitrogen content was 180 mg. per hundred cubic centimeters of blood. The electrocardiogram showed prolongation of the PR interval, left axis deviation and the T wave in all three leads in a direction opposite to that of the main ventricular complex. There was not much spread in the QRS complex, and no notching was seen. Necropsy revealed markedly secondarily contracted kidneys. The heart was moderately hypertrophied. The coronary arteries were not much degenerated, and the myocardium was normal for the patient's age. The auriculoventricular node and bundle were relatively normal, but a short portion of the first part of the right bundle

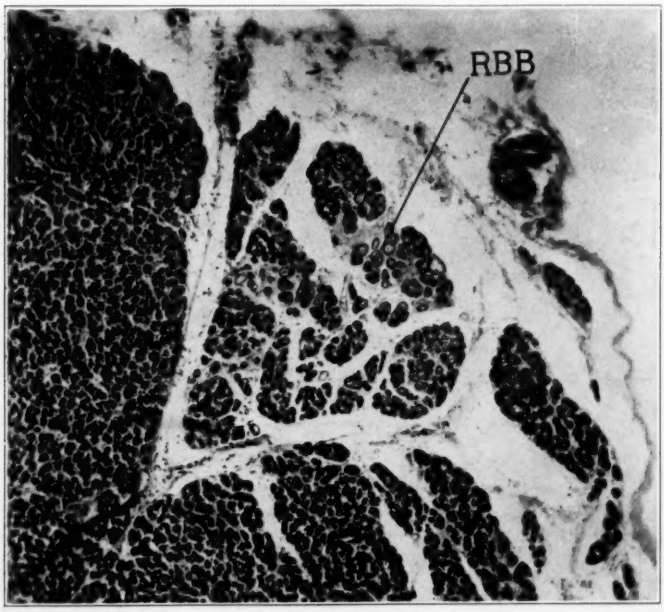

Fig. 20 (case 4).—Section 1,320, block 2, showing in horizontal cross-section the right bundle branch practically normal in its third portion; × 89.

branch was moderately fibrotic and the left bundle branch showed extensive but variable interstitial fibrosis, although the Purkinje fibers were well preserved.

Comment.—This case was studied because of the incomplete picture of bundle branch block. Some cardiologists would consider the electrocardiographic curves as those merely of preponderance of the left ventricle. However, the lesions of the bundle branches, especially of the left branch, would allow one to suggest that there was some reduction in the conduction time through the branches and certainly more

Fig. 21 (case 4).—Section 510, block 3, showing a portion of the left bundle branch embedded in dense fibrous tissue; × 140.

in the left than in the right. This relativity of involvement of the branches is important, since it must be rare for one branch alone to be diseased. Also, it does not seem to be necessary to assume that one or the other branch must be completely destroyed to produce distortion of the electrocardiographic curves.

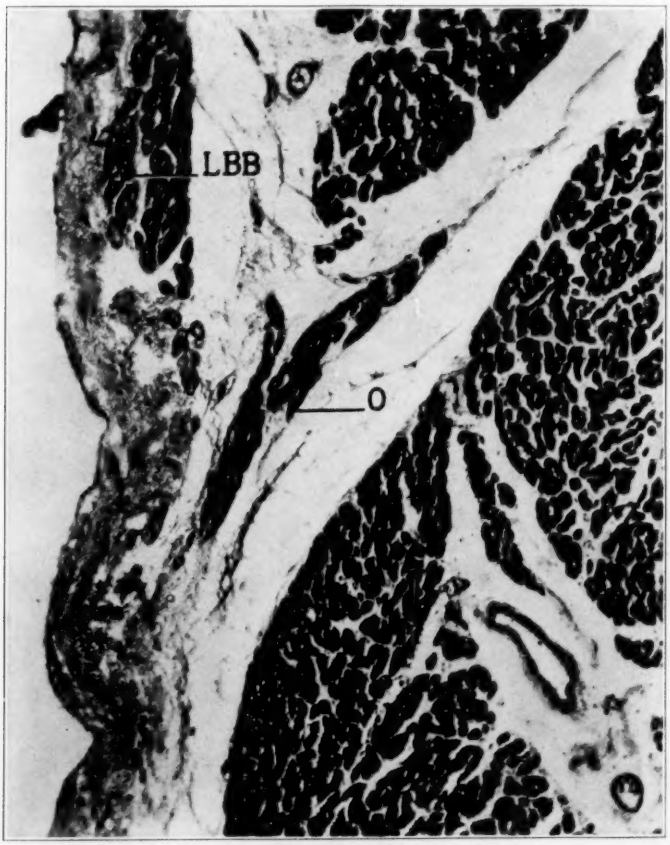

Fig. 22 (case 4).—Section 1,240, block 3, showing an offshoot (*O*) into the myocardium from the left bundle branch; × 92.

The pathogenic origin of the lesions of the conduction system in this case is not certain, but the etiologic factor of chronic renal disease with hypertension is clear. Although there was no advanced degree of disease of the coronary arteries, it appears that the involvement of the bundle branches was the result of impaired nutrition.

It is fair to point out that the electrocardiogram was made shortly before death, a fact which constitutes a weakness in relating the electrocardiographic picture to the lesions in the bundle branches.

The abortive offshoot of the left bundle branch observed in this case suggested the presence of communications directly into the myocardium from a bundle branch. This observation is reminiscent of the work of Cardwell and Abramson [153] (1931), Wahlin [154] (1932) and later Abramson and Margolin [169] (1936) in connection with animal hearts, but it is not conclusive. I have never seen unequivocal communications in the human heart either of the variety found in animal hearts or of the kind described by Mahaim [151] in the human heart, although I am willing to believe that minute communications do exist from one side of the septum to the other.

CASE 5 [170] (Army Medical Museum accession no. 52100).—*Clinical Record.*—A Spanish War veteran aged 53 years was found to have heart disease in November 1932, when he entered a hospital for repair of a ventral hernia resulting from appendectomy four years previously. In childhood he had smallpox, diphtheria, scarlet fever and mumps. He was told about four years before admission to the hospital that he had mild hypertension. The hernioplasty was followed by separation of the incision, later abscess formation in the wound and finally a prostatic abscess, which was accompanied with severe systemic symptoms and leukocytosis (25,000 leukocytes). His condition for a time was serious, but he eventually made a good recovery. His blood pressure at that time was 140 systolic and 86 diastolic. He had had attacks of tachycardia. An electrocardiogram made on Jan. 18, 1933, showed a heart rate of 144 per minute, a PR interval of 0.16 second, a QRS interval of 0.08 second, an S wave in all leads, the take-off of the ST segment a trifle elevated in leads II and III and a relatively low T wave in all leads.

After leaving the hospital he took a job requiring much exertion. Three months later the ventral hernia recurred. Dyspnea on exertion and attacks of precordial oppression and dull pain developed. However, he did not reenter the hospital until March 5, 1936. Examination showed the blood pressure to be 110 systolic and 68 diastolic; the heart sounds were normal, and the liver was not enlarged. Roentgenographic study revealed evidence of a chronic duodenal ulcer. The prostate gland was enlarged and boggy. He remained in the hospital five weeks, receiving prostatic massage and general treatment. On March 23, he had an attack of ventricular tachycardia (fig. 23 *A*), which ceased after the administration of 5 grains (0.33 Gm.) of quinidine sulfate. An electrocardiogram (fig. 23 *B*) then showed left axis deviation, with an inverted T wave in lead I and a QRS interval of 0.12 second. Lead IV showed a low take-off of the ST segment. He was discharged on April 11 in fairly good condition. However, he noted swelling of the feet almost immediately after discharge, when he resumed his work as a night watchman. Attacks of dyspnea, palpitation of the heart and precordial pain became more frequent. By November he could hardly get his shoes on because

169. Abramson, D. I., and Margolin, S.: A Purkinje Conduction Network in the Myocardium of the Mammalian Ventricles, J. Anat. **70**:250, 1936.

170. Major John G. Knauer gave me permission to use the records of this case and to study the heart.

of edema. Before the end of that month the edema involved the whole of both lower extremities. He began to expectorate blood-tinged sputum and became orthopneic. The abdomen became swollen. A physician gave him digitalis.

On December 5 he reentered the hospital, presenting the picture of advanced congestive failure. The blood pressure was 105 systolic and 60 diastolic. The heart sounds were weak. There was a peculiar impure quality to the first sound, which resembled the dull twang of a bowstring. Later a protodiastolic gallop rhythm appeared. The electrocardiogram was then different from the preceding one; there was much lower amplitude, and the QRS complex was much broader (0.16 second; fig. 23 *C*). Laboratory studies revealed evidence of mild renal insufficiency. The usual treatment was instituted, but all the manifestations of congestive heart failure progressed to an extreme degree, and death occurred on December 11.

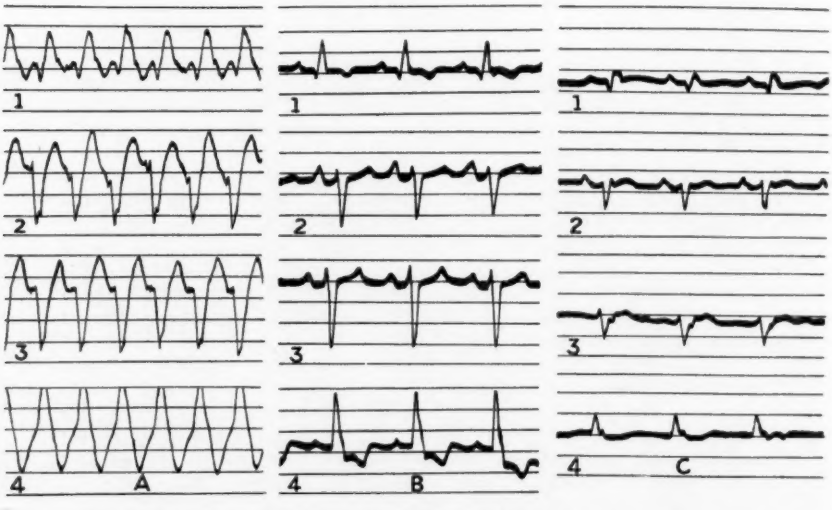

Fig. 23 (case 5).—*A*, paroxysmal ventricular tachycardia; *B*, left bundle branch block, with a QRS interval of 0.12 second, shown after the cessation of ventricular tachycardia, nearly nine months before death; *C*, a lower voltage and a QRS interval of 0.16 second a few days before death.

The following clinical diagnosis was made by Major Knauer: generalized arteriosclerosis, with severe coronary involvement; cardiac hypertrophy, with myocardial degeneration, fibrosis and herniation of the left ventricular wall and severe cardiac decompensation, secondary to coronary arteriosclerosis; moderate chronic suppurative prostatitis; large right ventral hernia; complete bilateral (large on the right and small on the left) direct-indirect inguinal hernia that was reducible; moderate chronic chorioretinitis of the right eye; moderate bilateral pinguecula; chronic ulcer of the duodenum; terminal bronchopneumonia of the lower lobes of the lungs, and moderate nephrosclerosis.

Necropsy.—Necropsy was performed by Major Don Longfellow approximately eight hours after death occurred. There was marked arcus senilis. The scleras

were icteric. The mouth was edentulous. There was severe pitting edema of the lower extremities and of the sacral region. The nail beds were slightly cyanotic. The right pleural cavity contained a large amount of thin brownish fluid, and there were delicate adhesions posteriorly. The lower and middle lobes of the right lung were covered with a fibrinous exudate. In the lower portion of the upper lobe there was a large blackish red infarct, and in the pulmonary artery leading to this area there was a thrombus which was firmly attached to the intima and which completely occluded the vessel. The lower portion of the lower lobe of the left lung was dark red, airless and apparently consolidated. The heart was moderately enlarged and was displaced to the left by the pleural effusion in the right hemithorax. The abdomen contained a large amount of thin clear straw-colored fluid. The liver weighed 1,700 Gm., and its cut surface presented a distinct "nut-meg" pattern. The kidneys were about normal in size and had a finely granular surface, with some superficial puckered scars. The cut sections showed cortical cysts, indistinct differentiation of cortices and pyramids and indistinct cortical striations. The prostate was much enlarged, and in the left lobe there was a honeycombed area; other portions of the cut surfaces were yellowish pink and homogeneous. The seminal vesicles were distended with thick granular material and were unusually thick walled. The first portion of the duodenum contained a small depressed ulcer, 4 mm. in diameter. There was moderately severe generalized arteriosclerosis.

Gross Examination of the Heart: The heart weighed 550 Gm. The lower anterior surface of the epicardium was roughened where adhesions to the pericardium had been separated. There was a normal amount of epicardial fat. All the chambers were dilated. The anterior descending branch of the left coronary artery was completely occluded below its first 2 cm. by an old yellowish thrombus for about 2 cm., beyond which it was occluded by a soft purplish clot. The wall was thickened and calcified. The lumen of the portion proximal to the thrombus was dilated. The first 3 cm. of the circumflex branch of the left coronary artery was greatly dilated and sclerotic and was filled with a fresh thrombus; beyond this its lumen was small, and the wall was asymmetrically thickened. The right coronary artery was only moderately sclerotic and was patent throughout. The left ventricle was dilated, grade 3, with a rounded apex, and its papillary muscles were moderately hypertrophied. The lower half of the interventricular septum showed a deep depression filled with an old mural thrombus (fig. 24). The upper edge of this depression ran obliquely downward from front to back toward the apex. The lower portion of the anterior wall and the rounded apical portion of the ventricle were thin and fibrous, being 2 mm. thick and containing practically no muscle. The thickness of the wall near the base of the ventricle was 1.8 cm. On cut section the myocardium here did not appear to be fibrotic. The endocardium of the left side of the interventricular septum between the aortic valve and the mural thrombus was smooth and glazed. The mitral valve was apparently normal except for moderate atheromatosis of the aortic cusp. The mitral orifice was 12 cm. in circumference. The aortic valve appeared to be normal, and the aortic orifice measured 7 cm. in circumference. The root of the aorta was moderately atherosclerotic. In the arch of the aorta there were numerous large calcified plaques, a condition which was maintained throughout the thoracic and abdominal portions. The right ventricle was dilated, grade 3. Its wall was 0.6 cm. thick in the upper half. In the apical region of its cavity a mural thrombus was loosely attached to the wall; its shape was that of a long curled cylinder, suggesting its origin in a vein. This appeared to be the source of the embolus in the right lung. The endocardium of this ventricle appeared normal. The

tricuspid valve was apparently normal, and the right venous ostium measured 13.6 cm. in circumference. The pulmonary valve also appeared to be normal, and its orifice measured 8.5 cm. in circumference.

Histopathologic Examination of the Heart: Five blocks of tissue were removed from the auriculoventricular and from the interventricular septum, the upper 3 of which included practically all the microscopically recognizable portion of the conduction system. These blocks contained the entire thickness of the septums. The upper 3 blocks were embedded in paraffin, and horizontal sections, 10 microns thick, were cut serially from above down. All the sections were mounted, and every tenth section was stained with Masson's trichrome preparation. There were 1,520 sections made from block 1, 1,720 from block 2 and 1,000 from block 3, making a total of 4,240 sections.

The auriculoventricular node and bundle and about 1 cm. of the bundle branches were included in the sections of block 1. The upper portion of the auriculo-

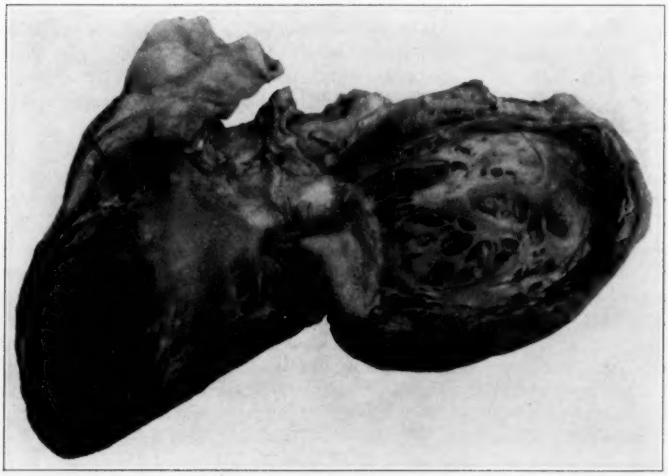

Fig. 24 (case 5).—The opened left ventricle, showing the scarred portion. A mural thrombus is seen in the depressed portion of the interventricular septum. The apical region bulges, almost aneurysmally.

ventricular node was composed of interlacing fibers that were much disrupted and that were separated by fibrous tissue and surrounded peripherally by fatty connective tissue containing little auricular myocardium. The lower portion of the node was more compact but contained somewhat more than the normal amount of fibrous and fatty connective tissue. The auriculoventricular bundle was also moderately infiltrated with fibrous connective tissue and was partly replaced by fatty connective tissue. Its capillaries were engorged with blood. The artery to the node and bundle was considerably degenerated, its wall being thickened and fibrous and its lumen narrowed by intimal fibrous tissue. The myocardium adjacent to the bundle was fibrotic. The auricular myocardium was fibrotic in the posterior half of the septum, and its largest artery had a thick, dense, fibrous wall and a small irregular lumen. The root of the tricuspid valve contained

numerous capillaries, plasma cells and fibroblasts. The first portion of both right and left bundle branch appeared moth-eaten because of fibrosis and fat invasion. The very first portion of the left bundle branch was extremely thin and almost not recognizable, but it rapidly became larger, although it remained fibrotic. The endocardium on the left side of the interventricular septum soon became thick and fibrous. The fibers of the left bundle branch were embedded in this fibrous tissue, and many of them appeared to have become necrotic and disintegrated because of compression; others appeared relatively normal. In some places there were relatively few Purkinje fibers remaining. The right bundle branch rapidly left its subendocardial position and became deeply intramyocardial. In most of block 1 about 15 per cent of the fibers were replaced by fibrous connective tissue. There was moderate patchy fibrosis of the interventricular septum. Only small vessels were seen in most of block 1. They were often surrounded by an abnormally thick zone of fibrous tissue; and the walls of some were moderately or even severely fibrotic, whereas others had fairly normal walls.

In the upper part of block 2 the left bundle branch became even more degenerated, the posterior half showing only a small number of fibers which appeared capable of functioning at all (fig. 25). The right bundle branch also became rapidly more fibrotic, until about 50 per cent of its fibers had been replaced by dense interstitial fibrous connective tissue (fig. 26). At no point, however, did the right branch appear to be as severely compromised as the left. The right branch, in fact, rapidly became less fibrous again, and as it approached the endocardium it became almost normal, remaining so as far as it could be followed subendocardially. The left branch, on the other hand, continued to be greatly degenerated by the invasion of fibrous tissue, although there was considerable variation in the degree of involvement. The surrounding connective tissue always remained dense, however. In block 2 the dense myocardial scar of an old infarct began to appear and grew larger with succeeding sections. The scar was patchy and most dense in the left side of the septum in its anterior half. The patches of scar tissue contained small thin-walled blood sinuses. The small arteries in the myocardium often had thick fibrous walls and small lumens. In the lower half of block 2 most of the anterior half of the left bundle branch had disappeared in the scar of the infarct. The posterior half of the branch had become larger and more cellular but was still embedded in dense fibrous tissue.

In block 3 the right bundle branch could not be found; and since in its upper part the right side of the septum was fairly normal, especially the endocardium, it was assumed that it had spread out normally beneath the endocardium and could not be recognized, as is frequently the case. The old scar in the septum grew larger, as did also the mural thrombus. The left bundle branch was present only in the posterior half and lower only in the posterior fourth of the septum. The branch was thicker, however, and contained more fibers on cross-section. As section 1,000 was approached the scar extended almost across the septum anteroposteriorly and involved most of the thickness of the septum, but more on the left than on the right half. The scar was not entirely solid but contained islands of myocardium. Only a small group of Purkinje fibers of the left branch finally remained at the very posterior part of the septum, and these were still embedded in fibrous tissue.

Summary.—A man aged 53 years was known to have had heart disease for four years and died of congestive heart failure. An electrocardiogram made ten months before death showed ventricular tachycardia; after cessation of the tachycardia an electrocardiogram showed left axis deviation, with an inverted T wave

in lead 1 and a QRS interval of 0.12 second. Another, made shortly before death, showed low voltage and a QRS interval of 0.16 second. The heart weighed 550 Gm., and all chambers were dilated. There was advanced coronary arteriosclerosis, with an old thrombus in the anterior interventricular artery and a fresh one in the left circumflex artery. An old infarct in the apical region of the left

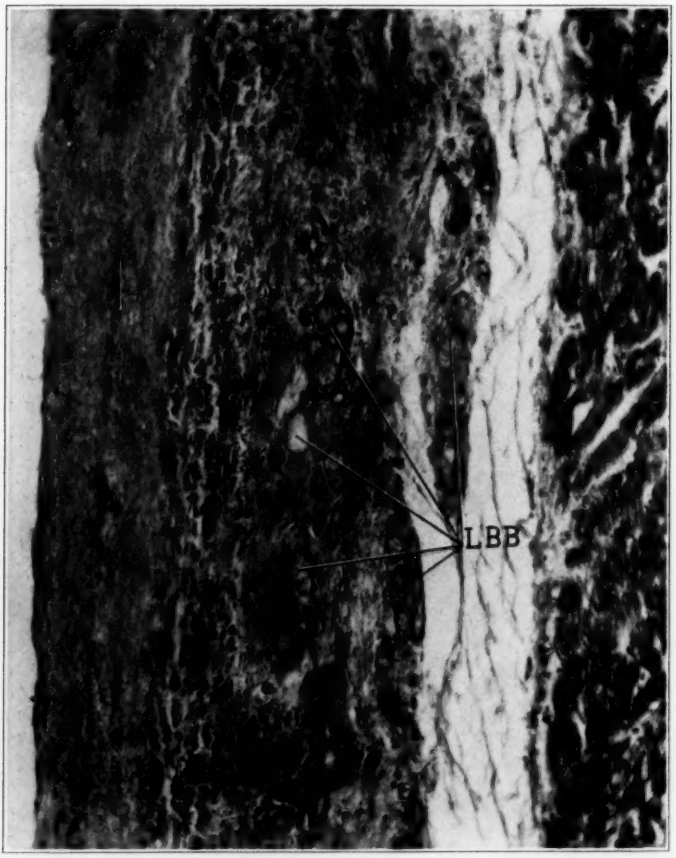

Fig. 25 (case 5).—Section 360, block 2, showing in horizontal cross-section a portion of the left bundle branch embedded in and almost completely replaced by fibrous tissue; × 137.

ventricle and in the lower anterior portion of the interventricular septum had caused marked thinning of these portions. A study of 4,240 serial sections of the conduction system showed that the auriculoventricular node and bundle were moderately fibrotic and partly replaced by fatty connective tissue. The right

bundle branch showed moderate fibrosis down to the middle of its intramyocardial portion, in which for a short distance fibrous tissue replaced about 50 per cent of its fibers. Beyond this point it was fairly normal. The left bundle branch was seriously degenerated by dense fibrous tissue in the subendocardial layer, especially in its upper half. In its lower half the anterior division had completely disappeared in the scar of the old infarct, whereas the posterior division, although still compromised by fibrosis, was not as much diseased as it was in its upper half.

Comment.—The electrocardiographic pattern in this case, i. e., the one made several months before death and after an attack of ventric-

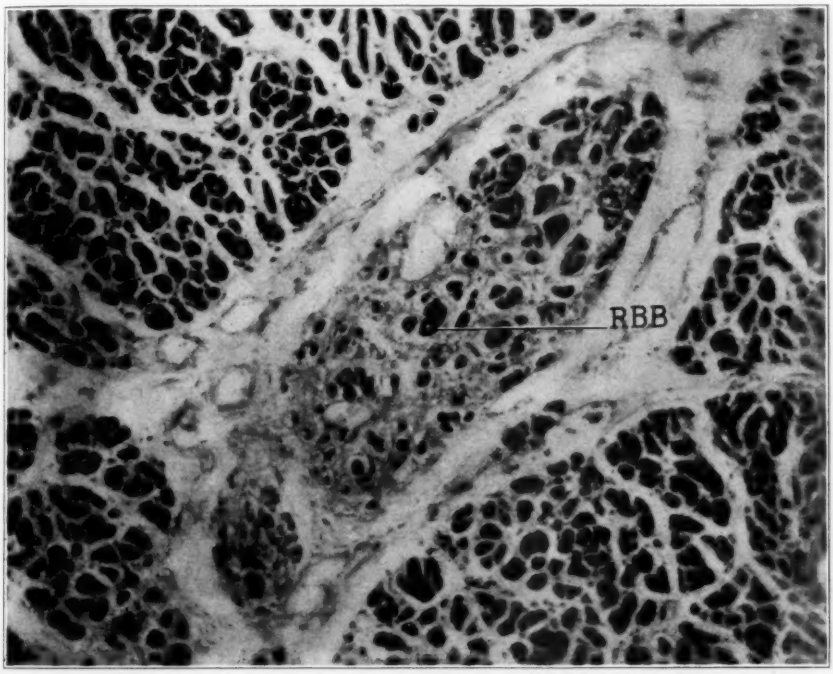

Fig. 26 (case 5).—Section 160, block 2, showing in horizontal cross-section the right bundle branch replaced in its upper portion by about 50 per cent by dense fibrous tissue; × 133.

ular tachycardia, represented merely an advanced stage of that in the preceding case. Although both bundle branches were diseased, there was no question as to the one more seriously affected. The left branch, while not completely destroyed at any one level, was so extensively degenerated throughout that, compared with the right branch, the impulses passing through it must have been greatly retarded. Conse-

quently, one is justified in assuming that the degeneration of the left branch played an important role in determining the electrocardiographic pattern.

The pathogenic factor in this case is clearcut, being advanced disease of the coronary arteries and old myocardial infarction. The electrocardiographic curves seen in this case are so frequently observed in cases in which the gross morbid anatomic picture is very similar that one may be pardoned for concluding that in most of these cases there is considerable degeneration of the left bundle branch.

CASE 6[171] (Army Medical Museum accession no. 52410).—*Clinical Record.*—The patient, a Negro aged 40 years, was admitted to the Hines Hospital, Hines, Ill., on March 11, 1936, for treatment of heart disease. He had had the usual diseases of childhood, pneumonia, "rheumatism" and gonorrhea. He became dyspneic in February 1935 and later had edema of the feet and a cough. He worked until July 1935 and after two weeks' vacation worked again for six weeks, after which he was unable to work. On admission to the hospital he was found to be moderately dyspneic and to have slight edema of the feet. The apex impulse was heaving and the heart moderately enlarged. Gallop rhythm was present at the apex. The cervical veins were distended, there was evidence of passive congestion of the lungs and the liver was palpable. The peripheral arteries were severely sclerosed. The heart rate was 110 per minute, and the blood pressure was 150 systolic and 125 diastolic.

An electrocardiogram, made on March 13, showed regular sinus rhythm; a rate of 120 per minute; a PR interval of 0.16 second; a QRS complex of moderate amplitude in leads I and III, of low voltage in lead II and of 0.14 second duration, grossly notched and with the main component upright in lead I and down in leads II and III, and a T wave that was intimately joined to the main complex, especially in leads I and III, and directed oppositely to them (fig. 27 *A*).

He received the usual treatment for congestive failure and was somewhat improved thereby. A second electrocardiogram, made on June 10, was similar to the first except that the QRS complex was upright in lead II. All the usual laboratory tests gave normal results. A roentgenogram showed moderate hypertrophy of the left ventricle.

From June 11, when he left the hospital, until Jan. 22, 1937, when he was readmitted, he remained in about the same condition. On his second admission to the hospital he was found to have more dependent edema and ascites. There was greater dyspnea. The apex impulse was felt in the left anterior axillary line. Gallop rhythm was present at the apex, and the heart rate was 100 per minute. The blood pressure at first was 110 systolic and 90 diastolic; later it was 90 systolic and 80 diastolic. A roentgenogram showed marked enlargement of the cardiac shadow, the aortic shadow measuring 7 cm., the greatest cardiac diameter 19 cm. and the transverse thoracic diameter 26 cm. There were large bullae on the dorsum of the feet, which were cold, and the skin of the legs was abnormally dark. Pulsations were not palpable in the left femoral artery, and none was palpable in the vessels of either foot. There were moderate anemia and moderate leukocytosis. The urine contained a heavy trace of albumin; the

171. Drs. Philip P. Matz and Edward W. Hollingsworth, of the Veterans' Administration, gave me permission to study the heart in this case and to make a report.

nonprotein nitrogen content of the blood was 120 mg. per hundred cubic centimeters. The electrocardiogram made on January 25 was essentially the same as the first one, made over ten months before.

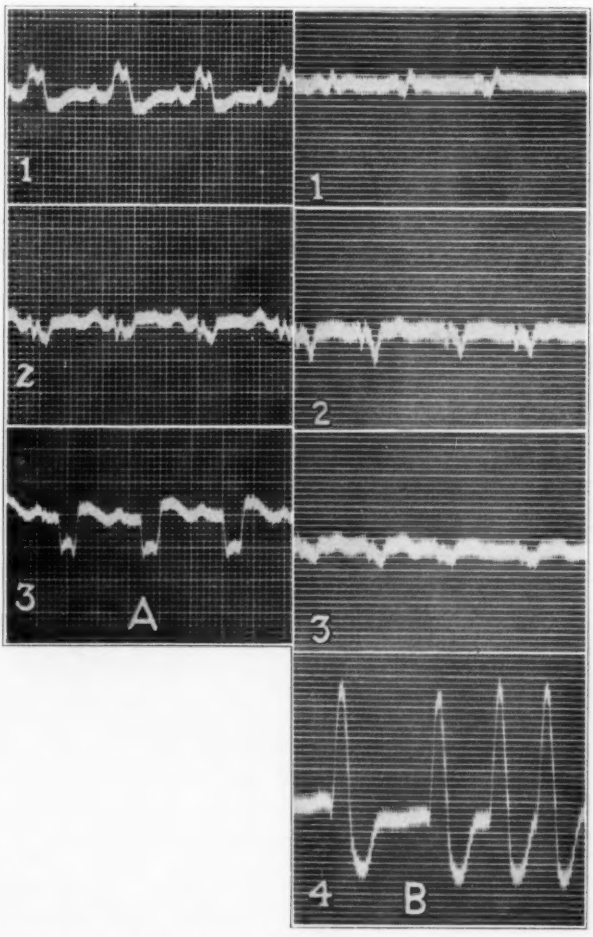

Fig. 27 (case 6).—*A*, left bundle branch block, with a QRS interval of 0.14 second, eleven months before death; *B*, auricular fibrillation, with low voltage except in lead IV and a QRS interval of 0.16 second, four days ante mortem.

The diagnosis of hypertensive heart disease and probable occlusion of the coronary arteries was made. It was also thought that there was thrombotic occlusion of both femoral arteries, with early gangrene of the feet. The course was rapidly downhill. The electrocardiogram made on February 5 was different

from the previous ones (fig. 27 *B*). It showed auricular fibrillation, low voltage except in lead IV, a grossly notched QRS wave of 0.16 second duration in leads I to III, a large QRS complex in lead IV and a T wave upright in leads I to III and inverted in lead IV. Death occurred on February 9.

Necropsy.—In addition to the cardiac abnormalities the following conditions were noted: extensive adhesions of the pleurae; abscesses in the lower portion of the upper lobe of each lung, containing grayish, foul-smelling material; ascites (about 1,000 cc. of clear fluid); whitish yellow plaques in the aorta, and adherent thrombi in both iliac arteries, the one in the right artery extending up to the

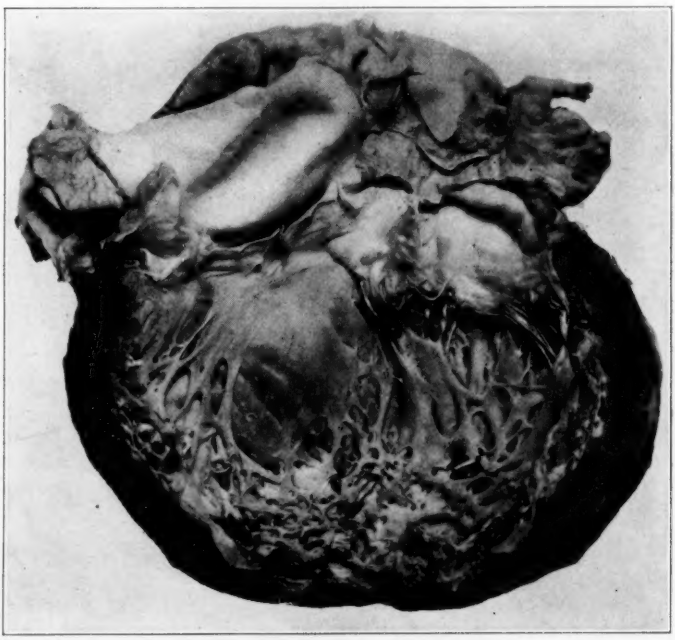

Fig. 28 (case 6).—The opened left ventricle, showing hypertrophy and extreme dilatation, with a small mural thrombus in the apical region.

bifurcation of the aorta and the one in the left extending below Poupart's ligament. The spleen weighed 210 Gm., the liver 1,560 Gm. and the kidneys 165 and 195 Gm., respectively.

Gross Examination of the Heart: The heart weighed 575 Gm. The pericardium was normal, with little fat. All four chambers were greatly dilated, the left ventricle tremendously so (fig. 28). In the greatly rounded apical portion of the left ventricle there was a mural thrombus, measuring 2 by 2 cm., with a slightly raised and roughened surface. It was firmly attached to the posterior wall. The endocardium over most of the left surface of the interventricular septum appeared normal, but it was thickened and presented a ground-glass appearance on the anterior wall of the ventricle, over the septum in the apical

region and in the vicinity of the thrombus. The wall of the ventricle near the base was 1.3 cm. thick, and on cut section the muscle did not appear abnormal. The aortic and mitral valves were apparently normal. The aortic ring measured 7 cm. in circumference and the mitral 9 cm. The root of the aorta was smooth walled. The left auricle contained a mural thrombus on its upper posterior wall, measuring 1 by 3 cm., and a smaller one was present in the auricular appendage. The wall of the right ventricle was 0.6 cm. thick near its base. Its endocardium appeared normal. The pulmonary and tricuspid valves were apparently normal, the ring of the former measuring 7 cm. in circumference and that of the latter 13.5 cm. The right auricular appendage was large, being 7.5 cm. long and 4.5 cm. wide. It was filled with thrombi, probably of antemortem origin. In connection with the eustachian valve there was a fibrous thread stretching vertically across the auricle for a distance of 4 cm. A small white thrombus was firmly attached to it at about its middle. The coronary arteries were a little thickened but were not calcified; their lumens were well open, except for agonal thrombi in both anterior and posterior interventricular arteries. The myocardium in general did not appear abnormal, and there was no gross evidence of old or recent infarction.

Histopathologic Examination of the Heart: The entire interventricular septum, including the lower portion of the auriculoventricular septum, was excised and divided by horizontal cuts into four blocks. The upper 3 blocks were embedded in paraffin and cut horizontally into sections of 10 microns thickness serially from above down. Block 4, which included the most trabeculated portion of the septum near the apex, was not cut because it would have been almost impossible to recognize the Purkinje fibers in it. From block 1, 970 sections were made; from block 2, 1,530, and from block 3, 1,400, making a total of 3,900 sections. All were mounted, and every tenth one was stained with Masson's trichome preparation.

The auricular myocardium was moderately fibrotic in patches, and the arteries therein were degenerated, with much intimal thickening and diminution in the size of the lumen. The auriculoventricular node was moderately fibrotic, as was also the auriculoventricular bundle. The very first portion of the left bundle branch was thin and contained only a few separated fibers. Too much importance should not be placed on such an observation, however, since this appearance does not necessarily indicate a pathologic condition. The beginning of the right bundle branch was moderately fibrotic, but like the node and main bundle it contained many normal-appearing conduction fibers. The right branch, however, soon became practically normal in appearance and continued so down to the portion which spreads out subendocardially. The left bundle branch was not completely interrupted at any level. However, it was definitely pathologic in much of its course. The fibers in many places were thin, vacuolated and embedded in dense fibrous tissue of the endocardium (fig. 29). The latter, however, was not much thickened. The best looking portion of the branch was the central part, which was thicker than the anterior portion, but its fibers also appeared much more vacuolated than normal. A large portion of this part of the branch entered a sheetlike layer of myocardium, which became separated from the main mass of the septum and gradually worked posteriorly, where it became the posterior division of the branch. As both anterior and posterior divisions broke up, their components entered trabeculae in which the Purkinje fibers formed fasciculi, many of which were embedded in dense fibrous tissue.

The myocardium of the septum had a few small scars scattered through it, but the great bulk of muscle was in good condition. The arteries in the septum were not as much degenerated as they were in the auricle near the central fibrous body.

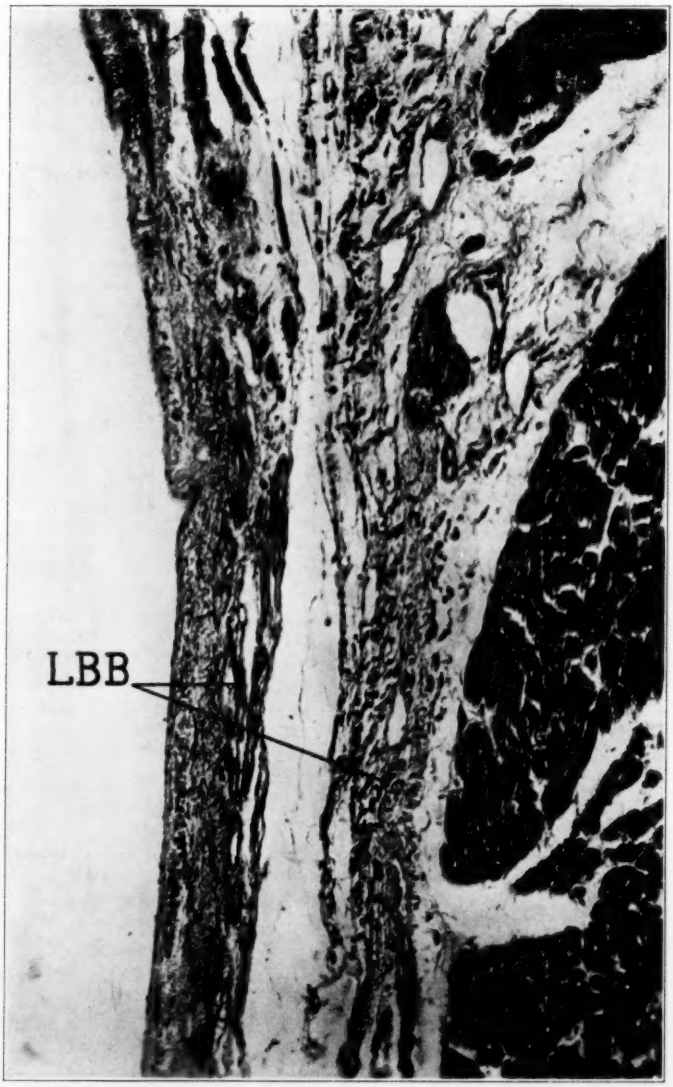

Fig. 29 (case 6).—Section 530, block 2, showing in horizontal cross-section a portion of the left bundle branch, with thin fibers largely embedded in dense fibrous tissue; × 140.

Summary.—A Negro aged 40 years had dyspnea for two years before he died. Edema appeared about six months after the onset of dyspnea. The blood pressure at first was moderately elevated but subsequently was normal. The heart was considerably enlarged. Manifestations of congestive heart failure gradually increased, and terminally there was evidence of renal insufficiency, with occlusion of the femoral arteries and gangrene of the feet. Three electrocardiograms made at intervals during the two years before death showed evidence of left bundle branch block. The electrocardiogram made two weeks before death showed auricular fibrillation and low voltage. The heart was found to be hypertrophied and dilated, especially the left ventricle, which contained a mural thrombus in its apex. The coronary arteries were only moderately sclerosed and contained only agonal thrombi. Histopathologic study revealed small scars in the myocardium. The arteries were not very sclerotic except in the auricles near the central fibrous body. The auriculoventricular node and bundle were moderately fibrotic. The right bundle branch except at its origin, where it was moderately fibrotic, appeared practically normal. The left bundle branch was moderately degenerated but apparently not greatly compromised; much of it was embedded in fibrous tissue, and its fibers were more than normally vacuolated.

Comment.—I was greatly surprised in this case to find comparatively little damage to the left bundle branch. It was, however, much more degenerated than the right branch, which was only slightly altered. Had there been a larger scar in the septum one might have concluded that the original electrocardiographic curves were the temporary result of coronary occlusion, with infarction of the myocardium. One would certainly expect more severe degeneration of the left branch in this case than in the 2 preceding cases from a comparison of the electrocardiograms. If one assumes, to begin with, that the electrocardiogram indicates impairment of function of the bundle branch in this case, it is plausible to assume further that there may be greater impairment of function of a branch than is evident histologically.

GENERAL COMMENTS ON CASES STUDIED HISTOPATHOLOGICALLY

Certain points in connection with the 6 cases studied histopathologically stand out clearly. In all there was definite organic disease of the bundle branches, although it was least marked in case 6, in which one would have expected more involvement than was observed. Both branches were affected in each case, but it was possible always to state which of the two branches was more seriously affected. The lesion consisted of fibrosis in all cases. In 4 cases (2, 3, 4 and 6) the lesions of the branches appeared to be independent of adjacent lesions in the myocardium, although there were also myocardial lesions of importance in 2 of these (cases 2 and 3), undoubtedly of similar pathogenic origin. In cases 1 and 5 the main involvement of the branches was clearly due to their position in regions of myocardial disease. In most of the cases it seemed proper to attribute the pathologic condition of the bundle branch and myocardial disease to disease of the coronary arteries. At

this point it may be well to state that many hearts not showing disease of the bundle branches have been studied histologically as controls, so that the observations in most if not all these 6 cases are probably of significance in the production of certain at least of the electrocardiographic abnormalities.

Cases 1 to 3 are of great significance in that the electrocardiographic curves said by the American school to typify right bundle branch block were associated with complete destruction of part of the right bundle branch, although there was also severe involvement of the left branch. In cases 1 and 2 the lesions were definitely of rheumatic origin, and in case 3 such an etiologic factor also seemed probable. I believe the lesions affecting the bundle branches and the myocardium in all 3 cases were due to rheumatic arteritis, certainly in cases 2 and 3. The valvulitis in cases 1 and 2 probably had nothing to do with the disease of the bundle branches, and in case 3 there was no evidence of valvulitis.

In cases 4 to 6 it appears that the lesions in the left bundle branch were the more important in the production of certain at least of the electrocardiographic abnormalities. These abnormalities would be designated by the American school as evidence of disturbance of intraventricular conduction of the left bundle branch type. The 3 cases are examples of so-called degenerative cardiovascular renal disease. In cases 4 and 6 the degree of disease of the coronary arteries was not great, but in case 5 it was extreme, and the lesions in the bundle branches were due definitely to this. In all 3 cases the brunt of the cardiac strain was borne by the left ventricle. In case 4 the slight increase in intraventricular conduction time appeared to be due to extensive fibrosis compromising but not destroying the left bundle branch. This is therefore a case of incomplete left bundle branch block. In case 5 there appeared to be much greater destruction of the left branch, but one could not state with certainty that the branch was completely incapable of functioning. In case 6, in which a complete lesion was anticipated, the lesions observed did not appear sufficient to cause complete interruption of the passage of impulses through the branch. One might conclude with caution, therefore, that cases of complete cross-sectional destruction of the left bundle branch may be rare but that partial lesions compromising the function of the branch may be common and may produce electrocardiographic alterations typical of left bundle branch block.

In only 1 of these 6 cases (case 5) was it possible to state that there was complete destruction of the anterior division of the left bundle branch, as has been said by Mahaim [26] to be so common. Even in this case there was also great involvement of the posterior division. This was the only case in which there was severe sclerosis, with occlu-

sion of the large coronary arteries; of these the anterior descending branch was the most affected. In this case there was also considerable fibrosis of a portion of the right bundle branch, a point well explained by the vascular supply of the branches.

One might attempt to explain why the right bundle branch was the more seriously damaged in the cases of rheumatic disease and the left bundle branch in the cases of cardiovascular renal disease. Perhaps the arteritis of rheumatic etiology, involving more prominently the intramyocardial arteries than the large subepicardial ones, more often affects the entire thickness of the interventricular septum and would be more likely to destroy completely the right bundle branch in its intramyocardial portion than it would the subendocardial portion, i. e., the main portion of the extensive left branch. In cases of cardiovascular renal disease, which includes disease of the coronary arteries or arterial hypertension or both, the brunt of the strain, either vascular or hypertensive, is borne by the left ventricle; therefore, it is fair to assume that the nutrition of the left bundle branch would be much more likely to suffer severely than that of the right branch.

From a study of these 6 cases it appears that the amplitude of the ventricular complex is not entirely dependent on the state of the bundle branches in clinical cases.

COORDINATION OF DATA ON BUNDLE BRANCH BLOCK

A careful weighing of the experimental data on bundle branch block shows more points in favor of the newer terminology for electrocardiographic curves. The difference between the newer American and the older European concept, which involves mainly a reversal of terminology, is explicable on the basis largely of anatomic differences between man and the dog.

A review of the literature on bundle branch block reveals much confusion as to which electrocardiographic curves can properly be designated as typifying bundle branch block and as to which bundle branch is affected. Although the classic curves in cases of bundle branch block are accepted by all, there are many atypical curves of unexplained origin. The pathologist has not kept pace with the electrocardiologist even in connection with the classic curves.

A consideration of the large number of published reviews of series of clinical cases of bundle branch block leads to the following conclusions: Bundle branch block is not uncommon. It occurs much more commonly in persons of middle age and early old age. It is much more common in men than in women. It is often but by no means always associated with definite clinical or physical evidence of heart disease. Left bundle branch block is much more common than right bundle

branch block, but the latter is not as uncommon as was originally thought. Cases of transient, intermittent or "functional" bundle branch block are not uncommon. They usually indicate organic heart disease and would probably be more frequently observed if electrocardiograms were made more frequently in individual cases. A progressive change from normal curves to those indicating bundle branch block might also be observed more often if this were done. A sudden onset of permanent bundle branch block is rarely noted. The association of various degrees of auriculoventricular block with bundle branch block is not uncommon, and auricular fibrillation may also occur in association with it. Premature contractions are, of course, fairly common accompaniments. The prognosis is grave, but many patients have lived for several years after discovery of the condition.

The question as to where curves indicating ventricular preponderance end and those indicating intraventricular block begin is not settled, but it is probable that any increase in the QRS interval over 0.1 second is an indication of disease of one or both bundle branches. Ventricular strain may be important in many cases in determining the direction of the main ventricular complex and the T wave, particularly in leads I and III. The effect of the position of the heart on the form of the electrocardiographic curves should rarely be sufficient to cause much confusion in the interpretation of the curves.

The pathogenic factor in cases of bundle branch block is almost always disease of the coronary arteries, rheumatic or degenerative, or hypertension, as indicated by a review of the literature and the 16 cases reported in this article.

The histogenic factor in bundle branch block is mainly fibrosis due to disease of the coronary arteries or to subendocardial thickening due partly to stretching and strain from hypertension, but the studies performed have been confusing, largely in regard to which bundle branch was more severely affected. I shall not attempt to explain the discrepancies among the reports of various authors. Of these authors, Mahaim [26] has done the most careful and complete work. The fact that his conclusions uphold in the main the old terminology may be more a matter of interpretation of the lesions than of faulty technic.

The vascularization of the conduction system explains well why it is rare for one bundle branch alone to be affected.

The histopathologic study of the 6 cases reported in detail in this article shows that (1) bundle branch lesions are probably almost always bilateral; (2) the pathogenic factor is mainly disease of the coronary arteries or strain resulting from hypertension; (3) the morbid anatomic feature is fibrosis; (4) the new terminology of bundle branch block is more nearly correct for man than the old one, although the designation

as to right or left must be admitted to apply only to the branch more seriously damaged; (5) right bundle branch block is probably usually due to rheumatic arteritis or myocarditis, and left bundle branch block is usually due to so-called degenerative cardiovascular renal disease; (6) a bundle branch need not be entirely destroyed at any level in order to cause retardation of the rate of conduction of the impulse through it; (7) the form of the electrocardiographic curve depends at least partly on the relativity of the degree of damage of the two branches and the extent and severity of involvement of the more diseased branch, and (8) increased amplitude is not necessary for the diagnosis of bundle branch block.

There remain many questions yet unanswered in regard to bundle branch block: the pathogenic factor in the various types of bundle branch block or intraventricular block; the importance and effect of the location of the damaged region of the branch or branches; the alteration of the curves indicative of branch block by the extent and severity of the myocardial disease, the degree of heart failure and the relative weights of the ventricles; the form of the ST component of the electrocardiogram; the reason for the direction of the complexes in lead II, and many others.

SUMMARY AND CONCLUSIONS

A review of the essential literature concerning bundle branch block has been made.

Sixteen cases of bundle branch block, with necropsy data, have been reported.

Six cases of bundle branch block studied by means of serial sections through the conduction system have been reported.

Bundle branch block is usually due to disease of the coronary arteries, either rheumatic or degenerative, or to hypertension resulting in strain of the left ventricle and impairment of the nutrition of the endocardium and bundle branch.

Bundle branch block is usually associated with bilateral bundle branch lesions, although one branch is usually more seriously affected than the other and probably usually determines the essential form of the electrocardiographic curve.

The newer, or American, terminology is more nearly correct for bundle branch block in man, although it must be admitted that whether right or left is used to modify the diagnosis of this conduction disturbance, the adjective merely indicates the branch more seriously affected.

The uncommon form of bundle branch block, right bundle branch block, is probably usually due to rheumatic arteritis or rheumatic myocarditis.

The common form of bundle branch block, left bundle branch block, is probably usually due to degenerative cardiovascular renal disease, meaning coronary arteriosclerosis or arterial hypertension or both.

A bundle branch need not be entirely destroyed at any level in order to produce electrocardiographic alterations that may be designated as typifying bundle branch block.

An increased amplitude of the ventricular complex is not essential to the electrocardiographic diagnosis of bundle branch block.

Any increase of the QRS interval beyond 0.1 second may indicate lesions of the bundle branches.

Many questions remain unanswered in regard to bundle branch block, and many careful histopathologic studies must be made before most of them can be answered.

Most of the photographs used to illustrate this article were made by Roy M. Reeve, chief photographer of the Army Medical Museum.

UNUSUAL REACTIONS OF PATIENTS WITH HYPERTENSION TO GLYCERYL TRINITRATE

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Hypertension has long intrigued physicians. Arteriosclerosis, a condition commonly associated with hypertension, has been extensively and profitably studied both clinically and pathologically. Histologic studies of patients with hypertension, however, have yielded but little information concerning the mechanism of this malady. The few anatomic changes that do occur are usually ascribed to the changes secondary to elevation of the blood pressure. It might be better to consider hypertension as a kinetic or an altered physiologic expression of a diseased condition. Experiments illustrating altered or abnormal responses to a known or standard stimulus might then give some insight into this changed vascular state.

Following this line of reasoning, studies were begun. First a standard procedure or test was necessary. The amyl nitrite test of Stieglitz [1] appeared to fulfil the requirements, and it was tried. A small pearl of amyl nitrite (0.3 cc.) was crushed in a towel and held directly under the patient's nose. He was then told to take three or four deep breaths of the vapor; studies of the blood pressure were made at frequent intervals. In actual practice the test was easily made but was impossible to standardize. No 2 patients would have the same depth of respiration; in fact, in many cases the patient instinctively drew his head away from the crushed ampule or held his breath, factors that precluded the inhalation of a known concentration of amyl nitrite.

A tablet of glyceryl trinitrate was then placed directly under the tongue, thus insuring a more definite administration of the drug. After a few patients had been tested by this method, severe reactions, viz., nausea, vomiting, collapse and the involuntary passage of urine, were noted. They appeared so alarming that it was decided to study their nature and frequency.

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1. Stieglitz, E. J.: Arterial Hypertension: Evaluation of the Prognosis, Arch. Int. Med. **46**:227-235 (Aug.) 1930.

METHOD

Fifty patients with essential hypertension and hypertensive heart disease were chosen from the outpatient dispensary. None of them had ever been given any nitrites in the past. They were admitted to the hospital the evening before the test so that they had twenty hours of complete rest in bed. The remainder were taken directly from the dispensary and put at complete rest in a recumbent position until three successive blood pressure readings taken at five minute intervals were within 6 mm. of mercury. This was called the basal blood pressure. It usually took from one-half to one hour to reach this low fixed level of blood pressure. All patients were given this preliminary period of rest and quiet before any test was performed. After one test was finished another rest period was given until a satisfactory blood pressure level was reached before the second test was begun.

The Hines-Brown cold water test[2] was first given. The patient's hand was immersed in water at 3 C. for exactly one minute. Great care was taken in moving the basin containing the ice water mixture to and from the patient so as to minimize his muscular movements. Two blood pressure readings were taken while the hand was in the water, the first one thirty seconds after immersion and the other just before withdrawal. After the hand was removed from the water, estimations of the blood pressure were made every thirty seconds for three minutes and thereafter for ten minutes. At the end of this period the blood

Fig. 1.—The capillary pipet which made possible the administration of accurate doses of spirit of glyceryl trinitrate.

pressure had usually returned to its basal level. In those few in whom it had not, a short rest period restored basal conditions.

An alcoholic solution of glyceryl trinitrate (spirit of glyceryl trinitrate) was used in all experiments to avoid the uncertain and irregular absorption of the drug that followed the use of the tablets. It was given directly under the tongue by means of an accurately graduated pipet (fig. 1). The glyceryl trinitrate content of the solution was assayed chemically by Dr. Clarence W. Muehlberger, Cook County toxicologist and toxicologist for the department of pharmacology of the University of Illinois College of Medicine, who also advised with us concerning this work. There were 8.2 mg. of glyceryl trinitrate per cubic centimeter of solution. Except when actually used, this solution was kept in a glass-stoppered bottle in the refrigerator. Estimations of the blood pressure were made every half minute for ten minutes or until a fairly stationary level was reached. Subjective symptoms were recorded as they were mentioned by the patient, as were also the objective signs. Inferential questioning was avoided, since this might have colored some of the responses. Sixteen patients were given second and larger doses of the drug, and 4 were given third and still larger doses in an attempt to measure the quantitative responses of successive depressions in blood pressure.

2. Hines, E. A., and Brown, G. E.: The Cold Pressor Test for Measuring the Reactibility of the Blood Pressure: Data Concerning Five Hundred and Seventy-One Normal and Hypertensive Subjects, Am. Heart J. **11**:1-9, 1936.

Peripheral vasodilatation, the well known and typical nitrite reaction, led us to study the peripheral vascular changes. In 12 patients the finger plethysmograph of Johnson [3] was used. Responses were quite variable. Capillary activity was investigated by means of a modification of the Lewis histamine flare method.[4] Thirty-two patients were given 0.2 cc. of a fresh 1:1,000 solution of histamine phosphate subcutaneously. Readings were made five, ten, fifteen and twenty minutes after the injections. Three fifths of the group (32 patients) were recalled, and their capillaries were studied by direct inspection of the nailfold both before and after the administration of glyceryl trinitrate.

RESULTS

Of this group of 50 patients with hypertension, 9, or 18 per cent, had mild to severe reactions after the administration of glyceryl trinitrate. These distressing responses to a drug that is generally considered quite harmless justify their full report.

REPORT OF CASES

CASE 1.—E. O., a white woman aged 68, had a basal blood pressure of 220 systolic and 120 diastolic. Four minutes after 0.24 mg. (1/200 grain) of the standardized glyceryl trinitrate was placed under her tongue, the blood pressure fell to 170 systolic and 110 diastolic. A minute later the systolic reading was 70 mm., and six minutes after the drug was given the pressure could not be determined. She was unconscious and was covered with cold perspiration, and her skin was ashen gray. Syncope lasted for three minutes. Two minutes later the blood pressure was 106 systolic and 92 diastolic; she said she felt better than before she fainted, although she still had a slight feeling of impending death. Improvement gradually continued, so that twenty-two minutes after the drug was given she felt normal and the blood pressure was 124 systolic and 94 diastolic. Then she was told to move her arms and legs. Fifteen minutes after this exercise the blood pressure rose to 200 systolic and 118 diastolic (fig. 2).

CASE 2.—W. S., a white woman aged 68, had a basal blood pressure of 188 systolic and 122 diastolic. A slight fall in the blood pressure followed the giving of 0.4 mg. (1/150 grain) of the standardized glyceryl trinitrate solution. Three minutes later the blood pressure had returned to the basal level; five minutes after the drug was given it was 208 systolic and 110 diastolic, but she felt ill, her face was gray and her skin was cold and clammy. She continued to feel ill; she tried to vomit and became unconscious for two minutes. Seven minutes after taking the glyceryl trinitrate she suddenly regained consciousness, her color became good and the blood pressure was 188 systolic and 84 diastolic. The recovery was complete within twelve minutes (fig. 3).

CASE 3.—N. G., a Negress aged 52, had a basal blood pressure of 224 systolic and 124 diastolic. About two minutes after 0.4 mg. (1/150 grain) of the standard glyceryl trinitrate solution was given, this patient fell ill, was restless and tried to get out of bed. This disturbed the arm cuff so that consecutive readings were impossible, although the arm cuff was replaced as soon as possible. Five and a

3. Johnson, C. A.: Studies on Peripheral Vascular Phenomena: A New Device for a Study of Peripheral Vascular Phenomena in Health and Disease, Surg., Gynec. & Obst. **55**:731-737, 1932.

4. de Takáts, G.: The Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities, Arch. Int. Med. **48**:769-785 (Nov.) 1931.

half minutes after the drug was given, the blood pressure was 176 systolic and 106 diastolic, and she had a severe headache. During the next five minutes the blood pressure gradually fell to 128 systolic and 84 diastolic. Then she became ill, muttered incoherently, moaned feebly and tried to vomit. As the pressure fell

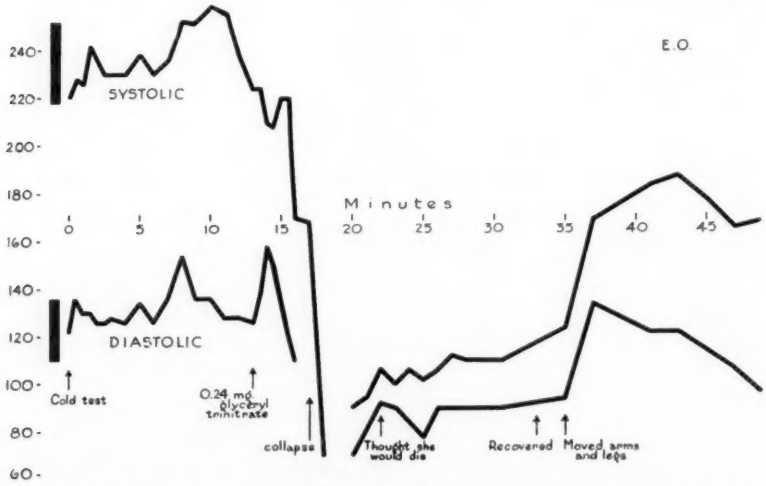

Fig. 2 (case 1).—A marked fall in blood pressure occurred after 0.24 mg. of glyceryl trinitrate was administered and a severe reaction occurred. The black blocks to the left represent the range of the patient's blood pressure before a basal level was reached.

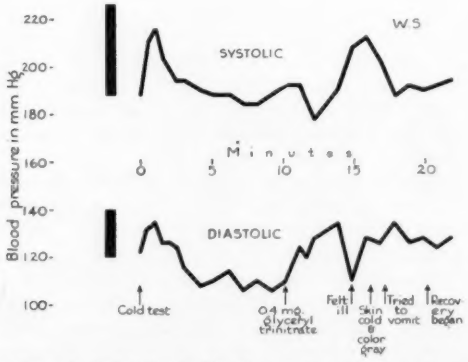

Fig. 3 (case 2).—A slight rise in blood pressure and a severe reaction occurred after the administration of glyceryl trinitrate.

to its lowest point (118 systolic and 74 diastolic), the nausea disappeared, and the headache "wasn't bad." Inhalation of aromatic spirit of ammonia produced no rise in blood pressure, whereas movements of the arms and legs caused a marked increase (fig. 4).

CASE 4.—I. B. N., a 57 year old white woman, had a basal blood pressure of 176 systolic and 106 diastolic. She was given 0.4 mg. (1/150 grain) of the standard glyceryl trinitrate solution. Three minutes later the blood pressure fell to 134 systolic and 112 diastolic, its lowest value; then it gradually rose.

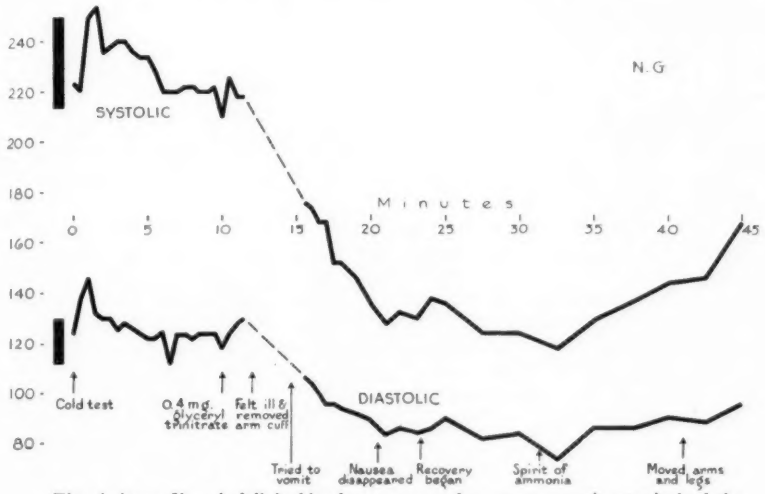

Fig. 4 (case 3).—A fall in blood pressure and a severe reaction typical of the effects of nitrites occurred.

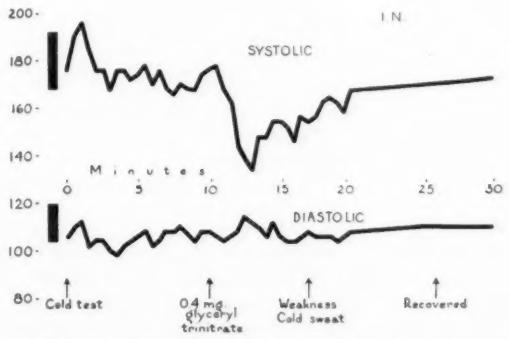

Fig. 5 (case 4).—A mild reaction and no appreciable alteration of blood pressure were noted after the administration of glyceryl trinitrate.

Seven minutes after the test was begun she complained of severe throbbing in the epigastric area, fulness in the region of the liver, headache and dizziness. Subsequently, she became extremely weak, perspired profusely and was soon covered with a cold sweat; however, her pulse was full and bounding. Within five minutes there was rapid and complete recovery. A second dose of 0.65 mg.

(1/100 grain) of glyceryl trinitrate was given. Although there was a lower and a more sustained fall in blood pressure, scarcely any symptoms were present except the abdominal pulsation.

CASE 5.—M. W., a white woman aged 45, had a basal blood pressure of 250 systolic and 120 diastolic. A tablet of glyceryl trinitrate, 0.6 mg. (1/100 grain), was placed under her tongue, and seven minutes later she complained of faintness and nausea. Shortly afterward she became unconscious and made repeated retching and vomiting movements, succeeding in bringing up only a small quantity of bile-tinged mucus. During this time, about five minutes, she was ashen gray and had shallow respirations and cold, moist skin. Urine was passed involuntarily. Artificial respiration and spirit of ammonia were used to revive her. After twenty minutes she recovered completely, and an hour later she was induced to take 0.2 mg. (1/300 grain) of glyceryl trinitrate. A slight headache was the only effect of this second dose of the drug.

CASE 6.—E. F., a 47 year old white man, had a basal blood pressure of 150 systolic and 90 diastolic. Seven minutes after a tablet of glyceryl trinitrate, 0.6 mg. (1/100 grain), was given to him, he complained of being dizzy, mumbled a few words about approaching illness and fell forward from his chair. The syncopal attack lasted for three minutes, when he suddenly opened his eyes and asked what had happened. There was complete recovery fifteen minutes after the drug was given.

CASE 7.—J. L., a 47 year old white man, with a basal blood pressure of 160 systolic and 95 diastolic, was given a tablet of glyceryl trinitrate, 0.4 mg. (1/150 grain), and seven minutes later he complained of vertigo, pounding in his head and nausea. He raised a small amount of bile-tinged vomitus but within twenty minutes had recovered completely.

CASE 8.—A. T., a white woman aged 51, with a basal blood pressure of 198 systolic and 115 diastolic, had been tested with 0.4 mg. (1/150 grain) of glyceryl trinitrate previously and had suffered only slight throbbing in the head. She was recalled to the laboratory and given 0.4 mg. (1/150 grain) of the drug preparatory to a study of changes in the capillary bed of the nail fold. Cyanosis, nausea and fainting occurred seven minutes after the drug was given. During this interval there had been a period of increased capillary flow, followed by the appearance of more capillary loops per field of observation. It was followed by a cessation of flow through the capillaries, and for fully two minutes before the reaction occurred there was cessation of flow through the capillary loops. Her symptoms were so alarming that several injections of 0.5 cc. of 1:1,000 epinephrine hydrochloride had to be given. She soon regained consciousness and felt better. Eight minutes later, or fifteen minutes after the glyceryl trinitrate was given, the blood pressure was 115 systolic and 74 diastolic. Complete recovery speedily followed.

CASE 9.—S. H., a white woman aged 39, had a basal blood pressure of 220 systolic and 110 diastolic. She had previously been tested with 0.4 mg. (1/150 grain) of glyceryl trinitrate but showed no reaction. Four minutes after she was given 0.2 mg. of the standardized glyceryl trinitrate solution, she felt "funny." A few seconds later she slumped forward in her chair, and at five minutes the blood pressure was 230 systolic and 124 diastolic. Within the next three minutes two fields of capillaries in her nailfold were found to be inactive. Attention was then turned to reviving the patient. Although inhalations of spirit of ammonia did not appear to raise the systemic blood pressure, it did hasten her recovery. Ten minutes after the onset of this reaction there was a slight activity of the capil-

lary bed. Recovery was well advanced by thirteen minutes after the collapse, the blood pressure was 218 systolic and 112 diastolic and normal capillary activity had been resumed.

Sixteen patients were given a second dose of glyceryl trinitrate, and 4 of them were given a third dose of the drug. This group were selected from the 50 because they showed a fall in blood pressure that was fairly typical of a nitrite reaction, but they did not give any reactions. The blood pressure readings of this group averaged 220; an initial average dose of 0.4 mg. ($\frac{1}{150}$ grain) of glyceryl trinitrate produced an average fall of 21 mm. in the systolic pressure, an average second dose of 0.6 mg. ($\frac{1}{100}$ grain) produced an average fall of 16 mm. and the 4 patients who received a third dose of the drug showed about the same depression of blood pressure as that after the second dose.

Posture appeared to affect the appearance of these reactions. The more severe reactions occurred when the patient was tested while in a sitting position (cases 5 to 9), and less severe reactions took place while he was in a recumbent position (cases 1 to 4). Also in several cases the patient who had a mild reaction while in a prone position showed a slight secondary reaction when he got up from the examining table. This could not be ascribed to muscular activity, since we frequently had each patient who had had such a reaction exercise his arms and legs after he recovered from his reaction but while he was still on the table. No secondary reaction was ever observed after this type of exercise.

A wide variety of responses followed the application of the Hines-Brown cold pressor test. A rise of from 0 to 9 mm. in systolic blood pressure occurred in 9 cases, a rise of from 10 to 19 mm. in 13 cases and a lowering of 24 mm. in blood pressure in 1 case. Twenty patients, or 40 per cent of this group, showed a normal response; 14 patients, or 28 per cent, showed a preorganic hypertensive response, and 12 patients, or 24 per cent, showed an organic hypertensive response. Seven of the 9 patients who had a severe reaction were given the pressor test. Unfortunately we were unable to obtain readings for the other 2 (cases 5 and 6). Maximal systolic rises were 22, 28, 32, 20, 12, 12 and 0 mm. No correlation between the height of the rise after the cold water test and the severity of the reaction after the giving of glyceryl trinitrate was possible. In fact, earlier tests usually gave greater elevations of blood pressure than later ones. This was due to the increasingly greater care that was taken to minimize the muscular movement of the patient. In later experiments the patient's hand was passively placed in the basin of ice water that had been brought to his bedside.

Tracings of arterial pulse waves, taken with the Johnson plethysmograph, showed no regular or typical reactions to glyceryl trinitrate; on the contrary, many of the patients showed a diminution or absence

of pulse waves. Neither was the histamine flare test of any value, as a great majority of the patients tested showed normal responses. There was no constant association of the size or the type of wheal, the area of erythema, the extent of the hypertension or the degree of tortuosity of the vessels. It appears that the capillary damage must be severe before the histamine reaction is impaired.

Studies of the capillaries were also made for the same 32 patients who were given the histamine test. The nailfold was used, and five to ten minutes was spent in an initial study of capillary activity. While the patient's hand was still in position under the microscope, 0.2 mg. ($\frac{1}{260}$ grain) of the standardized solution of glyceryl trinitrate was placed under his tongue. Observation of the capillary field was almost constant save for this slight interruption. In the majority of cases there was an increased rate of flow through the capillaries of the skin several minutes after the drug was given, unaccompanied by any change in size of either the arterial or the venous limb. After ten to fifteen minutes the flow returned to normal. In 3 cases a decreased rate of flow followed the taking of the drug. In only a few cases (4 patients) did complete blanching, i.e., disappearance of the vessel, occur. More commonly there would be a decrease in capillary flow, then the cells remained stationary in the vessel and blanching was not present. Here and there a space would appear behind the mass of cells on the arterial side, and the cells would proceed through the venous limb, thus emptying the vessels.

Another interesting observation was the simultaneous reaction of pairs of capillary loops. In some fields these paired vessels could be easily detected by their synchronous acceleration, slowing and cessation of blood flow in contrast to the other capillaries that did not present identical variations. Some of these paired vessels could be traced to a single common arteriole, a more deeply embedded vessel.

COMMENT

Inhalation of amyl nitrite for the relief of pain in angina pectoris was first advocated by Lauder Brunton, in 1867. Since that time glyceryl trinitrate has been recommended for more than forty-six ailments.[5] At present, however, its usage is restricted mainly to hypertension and angina pectoris. Its use has been suggested for seasickness,[6]

5. Merck, E.: Nitrite und Nitroverbindungen: Wissenschaftliche Abhandlugen aus den Gebieten der Pharmakotherapie, Pharmazie und verwandter Diziplinen, Darmstadt, E. Merck Chemische Fabrik, 1920, no. 38.

6. Pearcy, J. F., and Hayden, D. B.: Preliminary Report on Sodium Nitrite Therapy in Seasickness, J. A. M. A. **90**:1193 (April 14) 1928.

thromboangiitis obliterans,[7] cyanide poisoning,[8] acrocyanosis [9] and spasmodic conditions of the stomach and colon,[10] as the result of favorable experimental evidence. Recently, it has been effectively employed for the relief of pain and colic after cholecystectomy by McGowan, Butsch and Walters.[11]

There is a prevailing opinion among the members of the medical profession that glyceryl trinitrate is harmless. Stieglitz [1] has said: "The frequency with which amyl nitrite or nitroglycerine are administered with impunity in angina pectoris indicates strongly that the risk is minor if it exists at all." Unpleasant and even alarming symptoms had been recognized by the earlier writers, but the doses of glyceryl trinitrate were of the order of 6 mg. (1/10 grain). The fatal cases of nitrite poisoning followed the ingestion, either accidental or intentional, of large quantities of the drug. Nyström [12] described 2 cases of glyceryl trinitrate poisoning. At the end of an hour, cyanosis, dyspnea and delirium were present; coma and death followed within six hours. Necropsy showed marked filling of the vessels of the pia mater, venous sinus and cerebral cortex and injection of the optic thalamus and the ventricles. The kidneys and mucosa of the stomach, duodenum and colon were hyperemic, while the heart and lungs were normal. The normal appearance of the lungs was in keeping with the experimental results of Love and McGuigan,[13] who found strips of the pulmonary artery unaffected by glyceryl trinitrate.

The exact lethal dose of glyceryl trinitrate for man has not been determined for want of reliable observations. In many reports, mention is made of the fact that part of the drug had been lost by emesis prior to absorption, making definite deductions impossible.

In Germany glyceryl trinitrate has been used extensively. It was for awhile in favor, only to fall into disuse. Neither lack of experience nor improper preparations of the drug could be blamed, but it was felt that the drug was highly poisonous and too dangerous. This period was followed by a number of reports which showed that the toxicity

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7. Schlesinger, H.: Die Prognose der Thromboangitis Obliterans, Klin. Wchnschr. **9**:2112-2114, 1930.

8. Hanzlik, P. J., and Richardson, A. P.: Cyanide Antidotes, J. A. M. A. **102**:1740-1745 (May 26) 1934.

9. Cortés, C.: Intermittent Claudication: Treatment; abstracted, J. A. M. A. **91**:917 (Sept. 22) 1928.

10. Beams, A. J.: Nitrites in Spasmodic Conditions of the Gastro-Intestinal Tract, J. A. M. A. **97**:907-910 (Sept. 26) 1931.

11. McGowan, J. M.; Butsch, W. L., and Walters, W.: Pressure in the Common Bile Duct of Man, J. A. M. A. **106**:2227-2230 (June 27) 1936.

12. Nyström, C.: Om nitroglycerin, Upsala läkaref. förh. **2**:232-252, 1886.

13. Love, G. R., and McGuigan, H. A.: The Action of Nitrites on Pulmonary Circulation, J. Lab. & Clin. Med. **10**:882-884, 1925.

of the drug was not great. As much as 0.30 to 0.4 Gm. (5 to 7 grains) of glyceryl trinitrate was given to patients as a single dose without ill effect.[14] Again glyceryl trinitrate was in vogue, and its popular use in hypertension and angina was general.

Increased sensitivity to the drug has been infrequently mentioned. Amyot[15] reported on a patient who lost consciousness after contact with a piece of wood dipped in 1 per cent solution of glyceryl trinitrate. Two cases of collapse following the use of 0.65 mg. (1/100 grain) of the drug were described by P. D. White.[16] In a series of 110 patients receiving therapeutic doses of glyceryl trinitrate, 0.65 to 1.3 mg. (1/100 to 1/50 grain), four reactions were noted by Proger and Ayman.[17] All these reactions occurred in women between the ages of 58 and 67 who had hypertension. In each instance a rapid and marked drop in blood pressure, decreased radial pulse, cold perspiration, weakness, anxiety, restlessness and pallor were noted. All presented the picture of impending collapse. In 2 cases the blood pressure was so low that it could not be recorded. During an attack, complete heart block was demonstrated electrocardiographically in 1 case. Collapse following the administration of glyceryl trinitrate occurred in 3 cases reported by Sprague and White.[18] A therapeutic dose of the drug was presumed to have been given 1 man, but he had vomited and was unsconcious when first seen. A 68 year old woman was given 0.3 mg. (1/200 grain) of the drug for the relief of an anginal attack. Five minutes later she walked out of the room, but ten minutes later she tottered back and fainted. In the remaining case faintness, a small pulse, weak heart tones, ashen gray pallor and collapse were noted.

The serious nature of these reactions to therapeutic doses of glyceryl trinitrate led us to study their frequency and to seek a method of predicting their occurrence. As these reactions are similar to those of vasomotor collapse, it was thought that some method of testing vasomotor lability might give a clue to their nature. The cold water pressor test appeared to be suitable. Incident to the employment of this test, certain objections appeared. It was noted that the degree of movement

14. Stewart, D. D.: Tolerance to Nitroglycerin, J. A. M. A. **44**:1678-1679 (May 27) 1905. Hochaus, H.: Discussion über Arteriosklerose, Verhandl. d. deutsch. Cong. f. inn. Med. **22**:165-166, 1904. von Noorden, C.: Discussion über Arteriosklerose, ibid. **21**:152-154, 1904.

15. Amyot, cited by Merck.[5]

16. White, P. D.: The Significance and Treatment of Cardiac Symptoms, New England J. Med. **205**:907-914, 1931.

17. Proger, S. H., and Ayman, D.: Harmful Effects of Nitroglycerin, with Special Reference to Coronary Thrombosis, Am. J. M. Sc. **184**:480-491, 1932.

18. Sprague, H. B., and White, P. D.: Nitroglycerin Collapse—A Potential Danger in Therapy: A Report of Three Cases, M. Clin. North America **16**:895-898, 1933.

incident to that made by the patient when immersing his hand in water seemed to be reflected in the rise in blood pressure. The test was modified so that the basin of ice water was moved to the patient's hand and his hand passively moved into and from the ice water, minimizing the muscular movements. Considerably less pressor effect occurred after this new procedure was instituted. In other experiments the hand was kept in the ice water mixture for longer periods; some patients had ice applied directly to the dorsum of the hand. However, the response to cold seemed in no way to bear a relation to the previous degree of arterial tension; rather, it appeared to be proportional to the discomfort of the patient. Similar observations have been reported by Pickering and Kissin.[19]

Neither the histamine flare test nor the records of the pulse volume were of assistance in foretelling these reactions. Injection of histamine produces dilatation of the capillaries and venules of the skin. Using the Capps method [20] of measuring the tone of finer vessels, Wilkins, Haynes and Weiss [21] found the tone of the arterioles normal even during collapse induced with sodium nitrite. The Johnson finger plethysmograph presumably records changes in the pulse volume in the smaller arteries or arterioles. Our tracings from this apparatus gave no information concerning these reactions.

Reactions have been attributed to the sudden fall in blood pressure; however, we noted mild reactions with an elevation of blood pressure. A rise in systemic blood pressure after the administration of glyceryl trinitrate is not uncommon.[22] Burgess [23] found that the reaction to nitrites was not related to the degree or the rate of fall of the blood pressure. This was also our experience. Wilkins, Haynes and Weiss have placed the site of action of the nitrites on the venous side of the circulation. This action results in an increase in the venous volume, a pooling of peripheral blood in the venous system and a decrease in

19. Pickering, G. W., and Kissin, M.: The Effects of Adrenaline and of Cold on the Blood Pressure in Human Hypertension, Clin. Sc. **2**:201-207, 1936.

20. Capps, R. B.: A Method for Measuring Tone and Reflex Constriction of the Capillaries, Venules and Veins of the Human Hand with the Results in Normal and Diseased States, J. Clin. Investigation **15**:229-239, 1936.

21. Wilkins, R. W.; Haynes, F. W., and Weiss, S.: The Role of the Venous System in Circulatory Collapse Induced by Sodium Nitrite, J. Clin. Investigation **16**:85-91, 1937.

22. Loomis, H. P.: The Limitations of the value of Nitroglycerine as a Therapeutic Agent, M. Rec. **67**:411-413, 1905. Hewlett, A. W.: The Effect of Amyl Nitrite Inhalations upon the Blood Pressure in Man, J. M. Research **15**:383-393, 1906. MacNider, W. de B.: The Action of Nitrites on the Heart, Am. J. M. Sc. **135**:99-105, 1908. Dmitrenko, L. F.: Zur Pharmakodynamik des Nitroglyzerins, Ztschr. f. klin. Med. **68**:458-470, 1909.

23. Burgess, A. M.: The Reaction to Nitrites in the Anginal Syndrome and Arterial Hypertension, Ann. Int. Med. **5**:441-462, 1931.

the volume of circulating blood. We found that deep breathing and movements of the arms and legs, procedures that facilitate the return of venous blood to the heart, were most effective in preventing collapse. Inhalation of spirit of ammonia and artificial respiration were more reliable than injections of epinephrine in preventing reactions and in resuscitating these patients. Also these reactions are less severe when the patient is in a prone position than when he is upright. Any procedure that will prevent venous blood from pooling or accumulating in the venous channels and will thus decrease the volume of effective circulating venous blood will prevent or minimize these reactions.

SUMMARY

Severe reactions not infrequently follow the administration of glyceryl trinitrate to patients with hypertension. The nature and frequency of these reactions were studied. Fifty patients with essential hypertension or hypertensive heart disease were selected from the outpatient dispensary. A chemically assayed solution of glyceryl trinitrate was carefully administered directly under the patient's tongue with an accurately graduated pipet. All tests were made under standard basal conditions, and frequent blood pressure readings were made. Nine patients (18 per cent) showed reactions, i. e., nausea, vomiting, syncope, collapse and involuntary passage of urine and feces. These followed doses as low as 0.24 mg. ($\frac{1}{300}$ grain) and were more severe when the patient was sitting up than when he was recumbent. All the patients recovered completely within an hour. Four well known clinical procedures were applied in these cases in the hope of determining unusual vasomotor lability. The Hines-Brown test, the histamine flare test, changes in the pulse volume and observations of the capillaries of the skin were of no assistance in predicting these reactions.

1853 West Polk Street.

ACUTE AND CHRONIC MEDIASTINITIS

A STUDY OF SIXTY CASES

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Acute and chronic infections of the mediastinum are of sufficient frequency and importance to deserve more attention than has been given them. This seems especially significant since with the development and improvement of surgical technic it is possible in many cases to bring about striking improvement and even complete cure. During the past few years I have had the opportunity of observing a group of patients with various types of mediastinitis, and at this time I wish to review this experience and report on other patients who have been observed at the Boston City Hospital.

PATHOGENESIS OF MEDIASTINITIS

Infection of the mediastinal tissues is always secondary to infection of the various structures of the mediastinum or to infection extending to the mediastinal tissues from other locations, such as the neck, spine, lungs, pleurae or abdomen. The paths of extension of foci of infection in the neck and mediastinum have been made the subject of special study and investigation recently by Lerche,[1] Lambert and Berry,[2] Furstenberg and Yglesias,[3] and Coller and Yglesias.[4] For purposes of discussion, abscesses of the mediastinum can be divided into those involving the anterior mediastinum and those involving the posterior mediastinum. In some cases of rapidly advancing infection the entire mediastinum is involved, and a localized abscess does not appear. This condition is frequently referred to as diffuse phlegmonous mediastinitis. The present

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1. Lerche, W.: Infected Mediastinal Lymph Nodes as a Source of Mediastinitis, Arch. Surg. **14**:285 (Jan.) 1927; Suppuration in the Posterior Mediastinum, ibid. **8**:247 (Jan.) 1924.

2. Lambert, A. V. S., and Berry, F. B.: The Mediastinum: Paths of Extension of Infection from Focus in Mediastinum, Arch. Surg. **14**:261 (Jan.) 1927.

3. Furstenberg, A. C., and Yglesias, L.: A Clinical Study with Practical Anatomic Considerations of Neck and Mediastinum, Arch. Otolaryng. **25**:539 (May) 1937.

4. Coller, F. A., and Yglesias, L.: The Relation of the Spread of Infection to Fascial Planes in the Neck and Thorax, Surgery **1**:323, 1937.

group of sixty patients were divided in accordance with the location of the process, as shown in the accompanying table.

Before discussing the cases it is well to review the paths of extension and the roentgenographic appearance in mediastinal infections. Familiarity with these two aspects of the condition is of great assistance in making a diagnosis.

Data Concerning Sixty Cases of Acute and Chronic Mediastinitis

	Total Cases	Recovery	Death
A. Abscess of anterior mediastinum			
I. Acute abscess depending on			
a. Osteomyelitis of sternum	1	..	1
b. Ulceration of larynx	4	..	4
c. Cellulitis of neck	2	2	..
d. Infarct of lung	1	..	1
e. Pneumococcic infection	1	1	..
Total	9	3	6
II. Chronic mediastinitis from			
a. Syphilitic mediastinitis	3	1	2
1. Tracheal stenosis; thrombosis of left innominate veins			
2. Thrombosis of superior vena cava			
3. Aneurysm of aorta; thrombosis of innominate veins			
b. Mediastinopericarditis			
1. Syphilis with aneurysm of aorta	1	..	1
2. Rheumatic heart disease with mitral stenosis	3	..	3
c. Cause undetermined	2	1	1
Total	9	2	7
B. Abscess of posterior mediastinum			
I. Acute abscess			
a. Perforation of esophagus by			
1. Foreign body	9	3	6
2. Carcinoma of esophagus	7	..	7
3. Aneurysm of aorta	2	..	2
4. Stricture of esophagus	1	..	1
5. Rupture of esophagus	1	..	1
6. Tumor of lung	1	..	1
b. Suppuration of lymph nodes	2	2	..
Total	23	5	18
II. Chronic abscess			
a. Abscess; tuberculosis	3	2	1
C. Acute diffuse mediastinitis			
I. Pneumonia	14	..	14
II. Peritonitis	2	..	2
Total	16	..	16
Total	60	12	48

PATHS OF EXTENSION IN MEDIASTINAL INFECTIONS

The diagnosis of a mediastinal abscess may depend, in part at least, on the manner in which the infection spreads. Indeed, in some cases the diagnosis may be obscured by the presence of an infection in an area adjacent to the mediastinum. As previously stated, the pathways of spread have been worked out by Lambert and Berry [2] and Furstenberg and Yglesias.[3] Lambert and Berry have pointed out that an abscess may spread upward into the fascial planes of the neck, downward into

the retroperitoneal connective tissue, posteriorly along the bodies of the vertebrae to the endothoracic fascia outside the pleura and the parietal pleura or through the broad ligaments of the lung beneath the visceral pleura and into the substance of the lung down the larger branches of the bronchial tree. An exudate in the anterior mediastinum dissects beneath the sternum and outside the anterior pleural reflexion. The abscess may also compress the esophagus or the trachea and bronchi and may actually rupture through these structures. Extension to the pleural cavity has also been observed.

ROENTGENOGRAPHIC APPEARANCE IN MEDIASTINAL INFECTIONS

Roentgen examination of the chest is of significance in the diagnosis of an abscess or of a chronic infection of the mediastinum. The changes consist of unilateral or bilateral triangular shadows superimposed on the cardiac shadow or of rounded or triangular shadows in the superior mediastinum. There may be, of course, an associated empyema or extrapleural abscess obscuring the pulmonary fields. When the abscess is in the superior mediastinum, the esophagus is displaced anteriorly. This can be seen under the fluoroscope, especially in the lateral view. When the abscess is lateral to the trachea, there is a unilateral rounded shadow, but the trachea is often not displaced. If a large abscess is near the bifurcation of the trachea, there may be some widening and compression of the bronchi, with pulmonary atelectasis.

The spine should be examined for signs of destruction in all cases of suspected posterior mediastinal abscess, since destruction is evidence of Pott's disease or of pyogenic or mycotic infection of the vertebrae.

The condition that is most likely to be confused with mediastinitis is a mediastinal pleural effusion or a mediastinal tumor.

In cases of mediastinal pleural effusion the shadows are triangular on either side of and continuous with the median shadows of the chest. No cardiac pulsation is seen in the abnormal shadow, and the heart or the lung may be displaced to the opposite side. The condition is almost always unilateral. In cases of paravertebral abscess the shadow is definitely separated from the posterior mediastinal pleural space and has its origin in the posterior thoracic wall. The shadow of the abscess is seen on both sides of the spine.

DIAGNOSIS

The diagnosis, then, will depend on the history of a condition which is capable of causing infection of the mediastinum, together with the symptoms and signs of infection of the mediastinum; familiarity with the paths of extension of such an infection, and the roentgenographic findings in the chest.

The roentgenographic findings in cases of chronic fibrous mediastinitis will vary, depending on the extent of the process and whether the pericardium is involved at the same time. In some cases there may be only a dense shadow extending beyond the costosternal borders or the hilus, irregular in outline, and not having the sharp, well defined borders of an abscess or tumor. The process is most conspicuous about the trachea and bronchi and extends to the central part of the lungs. During inspiration the heart is displaced upward.

ABSCESS IN THE ANTERIOR MEDIASTINUM

There were eight cases of abscess of the anterior mediastinum. Each abscess arose from an extension of an infection from the neck, larynx, sternum, lymph nodes or lung. In reports of one hundred and fifteen cases collected by Hare,[5] abscess in the anterior mediastinum was more common than abscess in the posterior mediastinum. In many cases the abscess followed an injury, such as fracture of the sternum, or an infection, such as erysipelas or some condition involving the respiratory tract. Most of the chronic abscesses were due to tuberculosis. Infection of the wound after an operation on the neck may be followed by mediastinal abscess.

Another rare cause of abscess in the anterior mediastinum is an infection following an operation involving the upper portion of the abdomen, such as cholecystectomy, or an infection of the gallbladder without surgical treatment. Such cases have been recorded by Whipple [6] and Kornblum and Osmond.[7]

When pus accumulates in the anterior mediastinum it tends to extend to the exterior, and it may present in the suprasternal notch or at the anterior border of the sternocleidomastoid muscle. It may gravitate down and cause a painful, tender area in the region of the xiphoid cartilage. On rare occasions such an abscess may present beneath the sternoclavicular region or may perforate into the costal interspaces in the parasternal line. An abscess which perforates is usually chronic and due to tuberculosis or actinomycosis.

The symptoms and signs of an abscess in the anterior mediastinum are those of an infection in this region. Pain is a conspicuous feature and is usually substernal and throbbing. There may be irritative phenomena, such as cough and pain on movement of the trachea. Swelling and edema of the neck and thoracic wall, with dilatation of the veins,

5. Hare, H. A.: Mediastinal Disease, Philadelphia, P. Blakiston's Son & Co., 1888, p. 96.

6. Whipple, A. V., in discussion on Lambert and Berry.[2]

7. Kornblum, K., and Osmond, L. H.: Mediastinitis, Am. J. Roentgenol. **32**:23, 1934.

may be conspicuous. In one case, after pneumonia which resolved spontaneously, there were signs of obstruction of the right innominate vein and swelling of the neck and right arm. Paroxysmal hypertension may accompany the abscess. Such a case was observed by McKinlay, Kinsella and Radl.[8]

On the whole, the signs of infection predominate, and the local signs may be indefinite, but when present they are due to compression and irritation of surrounding structures. Roentgenographic examination of the chest is important, since evidence of the presence of a supra-aortic structure which has displaced either the trachea or the esophagus posteriorly may be of great diagnostic assistance.

The following case illustrates the course of events when an abscess of the anterior mediastinum develops after an infection in the neck.

Case 1.—A 36 year old woman with symptoms of hyperthyroidism was admitted to the hospital, and thyroidectomy was performed. After the operation fever and signs of an infection in the operative wound developed. This condition persisted for fourteen days, when the temperature increased to 102 F. There were cough and a few rales in the left side of the chest posteriorly. A roentgenogram showed evidence of bronchopneumonia in the lower lobe of the left lung and some increase in the width of the shadow of the superior mediastinum. On the twentieth day after operation the temperature continued to be elevated, and the patient complained of severe substernal oppression, especially under the manubrium of the sternum. There was increased retromanubrial dulness, and the roentgenogram showed deviation of the trachea to the right, an increase in the supracardiac shadow and signs of consolidation of the lower lobe of the left lung. On the thirty-second day after the operation the wound in the neck was bulging somewhat, and roentgenograms continued to show widening of the mediastinum. A clamp was inserted into the superior mediastinum from the draining sinus in the neck, and a large amount of pus was evacuated. The pus showed hemolytic streptococci in pure culture.

After drainage of the abscess the temperature gradually declined, and the improvement was striking. Complete recovery followed within ten weeks after operation and within five weeks after drainage of the abscess. The course of the temperature is charted in figure 1.

Summary.—This case illustrates the course of events when a mediastinal abscess follows an infection of the neck. The symptoms and signs of infection were conspicuous for several weeks before there was evidence suggesting a mediastinal abscess. After drainage of the abscess, recovery followed promptly.

CHRONIC ABSCESS OF THE ANTERIOR MEDIASTINUM

Chronic abscess of the anterior mediastinum is due most often to tuberculosis. Fibrosis of the anterior mediastinum is due to the same cause, but, in addition, one must consider the possibility of syphilis.

8. McKinlay, C. A.; Kinsella, T. J., and Radl, R. B.: Acute Essential Hypertension Precipitated by Mediastinal Abscess, Arch. Int. Med. **54**:645 (Oct.) 1934.

Tuberculous abscess of the anterior mediastinum results from broken-down necrotic lymph nodes or from an extension of tuberculosis from the sternum or the lung. It may remain localized, perforate the thoracic wall, appear in the suprasternal notch or produce sinuses through the thoracic wall. When sinuses appear the disease may be confused with perforation of an infected dermoid cyst of the mediastinum or with actinomycosis.

The symptoms and signs are those of chronic infection, with evidence by physical and roentgenologic examination of a mass in the anterior mediastinum causing compression of blood vessels or swelling of the thoracic wall. There were no instances of chronic tuberculous abscess in the present group of cases.

CHRONIC DIFFUSE MEDIASTINITIS

Chronic fibrous mediastinitis arises in the same way as acute mediastinitis, but the etiology is somewhat different. It is caused by: (1) tuberculosis, (2) syphilis, (3) mycotic infection (actinomycosis or

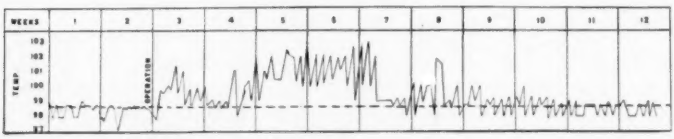

Fig. 1 (case 1).—Chart showing the temperature curve in a case of mediastinitis following thyroidectomy.

streptotricosis), (4) rheumatic fever, (5) pyogenic infection, (6) pneumonoconiosis and (7) chronic paragonimiasis.

The diagnosis frequently depends on associated lesions of the lungs, bones, heart, aorta, pericardium or other mediastinal structures. When such signs are not cleancut, the commonest features are those of compression of the superior vena cava or of the innominate veins, without evidence of a tumor or aneurysm of the aorta, and there is a comparatively long duration of the symptoms and signs, with few constitutional symptoms. When there are, in addition, signs of bronchial or tracheal stenosis, paralysis of the recurrent laryngeal nerves or pericarditis, the extent of the lesion may be postulated, and the etiologic factor may be suggested.

In nine of the sixty cases there was chronic fibrous mediastinitis. Four were instances of mediastinopericarditis; in one case the condition was due to syphilis and was associated with aneurysm of the aorta, and in three cases it was due to rheumatic fever, with associated mitral stenosis. In three cases the condition was due to syphilis; in one case there was associated bronchial stenosis, with resultant thrombosis of the left innominate vein, in one case there was associated thrombosis

of the superior vena cava and in one case there were associated aneurysm of the aorta and thrombosis of the left innominate vein. The cause of the mediastinitis in the other two cases remained obscure.

The following case illustrates the sequence of events in one of the cases of syphilitic mediastinitis, with bronchial stenosis and thrombosis of the innominate veins.

CASE 2.—A man aged 43 years complained of cough and swelling of the left arm. He had been well until one year before admission to the hospital, when there had developed a cough with expectoration of white mucoid sputum. He had dyspnea on exertion and at night, which was often relieved by expectoration. Two weeks before admission to the hospital he had some pain in the chest; it was substernal and radiated to the left axilla. He had noticed some swelling of the left arm.

Examination showed dilatation of the right jugular vein and swelling of the upper part of the left side of the chest and neck. The upper part of the left arm was swollen and edematous. All the signs of occlusion of the left internal jugular and of the left innominate vein were evident. There was no dilatation of the veins over the upper part of the chest. Examination of the heart revealed no abnormality. The retromanubrial dulness was not increased. The lungs were clear except for signs of partial obstruction of the bronchus leading to the upper lobe of the left lung, where there were high-pitched squeaking rales, suppression of the breath sounds and impaired resonance on percussion.

Roentgenograms showed no tumor mass in the superior mediastinum, and the aorta was of normal size and in normal position. There were increased shadows at the pulmonary roots, which were interpreted as being evidence of pulmonary fibrosis. Bronchoscopic examination showed narrowing and scarring of the left main bronchus but no tumor. The Wassermann reaction was positive. During observation the patient had two small pulmonary infarcts, which were diagnosed by the presence of cough, bloody expectoration, pain in the chest and a pleural friction rub.

Under antisyphilitic treatment he improved remarkably. The signs of vascular occlusion gradually diminished but did not subside. At the end of one year of observation he had gained weight and was greatly improved.

Summary.—A man with syphilis showed signs of bronchial obstruction and occlusion of the left innominate and jugular veins, with several attacks of pulmonary infarction. Remarkable improvement followed antisyphilitic treatment.

While syphilis is an infrequent cause of diffuse mediastinitis, it may be associated with: (1) an aneurysm of the aorta, (2) syphilitic tracheobronchial stenosis or (3) pericarditis, or (4) it may occur independent of these three lesions. In the cases in which syphilitic mediastinitis occurs independent of the first three conditions, the signs of occlusion of the superior vena cava or of the innominate vein predominate, since the anterior and the superior mediastinum are involved predominantly. Other structures that become constricted are nerves and large bronchi. The case reported by Knox[9] is an excellent example of this type of

9. Knox, L. C.: Chronic Mediastinitis, Am. J. M. Sc. **169**:807, 1925.

mediastinal disease, and Martland [10] has expressed the opinion that syphilis is one of the commonest causes of chronic mediastinitis.

In a recent review of the literature on thrombosis of the superior vena cava by Ochsner and Dixon,[11] it was reported that in no less than 19 per cent of the cases the condition resulted from syphilis and in 9.1 per cent of these syphilitic mediastinitis was the cause. In the other 10 per cent the condition was said to have resulted from phlebitis, and it is not unlikely that in many of these cases there was associated mediastinitis. In one of the cases listed in the accompanying table there was thrombosis of the superior vena cava, and in two others there occurred thrombosis of the innominate vein on the left side. In case 2 of the present series there was thrombosis of the innominate vein as well as an associated syphilitic lesion of the bronchus.

Examples of mediastinitis associated with syphilis of the trachea and bronchi were cited in Conner's [12] classic review of the subject. Usually the signs of an intrinsic lesion of the trachea or bronchi predominate, and occasionally palsy of the recurrent laryngeal nerve or occlusion of blood vessels occurs.

Cases of mediastinitis associated with aneurysm are not frequent, but in most instances the mediastinitis is localized about the root of the aorta. Sometimes, however, it is more diffuse and produces thrombosis of veins, as in one of the cases mentioned, or it is associated with pericarditis. These cases are discussed under the headings mediastinopericarditis.

MEDIASTINITIS ASSOCIATED WITH PERICARDITIS—MEDIASTINOPERICARDITIS

Under the heading mediastinopericarditis there is often described a group of cases in which there are signs of adherent pericardium as well as mediastinitis. In the present group there were four cases of chronic diffuse mediastinitis associated with chronic adhesive pericarditis. In one the mediastinitis was presumably the result of syphilis, since the condition was associated with an aneurysm of the arch of the aorta. In the other three cases the mediastinopericarditis was associated with mitral stenosis and probably resulted from a rheumatic infection. In all the clinical features were those of cardiac insufficiency with congestion.

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10. Martland, H. S.: Diseases of the Mediastinum: Certain Anatomical Considerations, in Diseases of the Respiratory Tract, Eighth Annual Graduate Fortnight of the New York Academy of Medicine, Philadelphia, W. B. Saunders Company, 1936, p. 365.

11. Ochsner, A., and Dixon, J. L.: Superior Vena Caval Thrombosis: Review of the Literature and Report of Cases of Traumatic and Infectious Origin, J. Thoracic Surg. **5**:641, 1936.

12. Conner, L. A.: Syphilis of Trachea and Bronchi, Am. J. M. Sc. **126**: 57, 1903.

In the case of syphilis the signs of aneurysm of the aorta were associated with heart failure which had resulted from compression of the pulmonary artery and hypertrophy and dilatation of the right ventricle. The conspicuous feature of the heart failure was recurrent ascites. It is doubtful whether the adherent pericardium played any part in the circulatory failure, since the heart was of normal size, the pericardial adhesions were not thick and the cardiac muscle was not compressed. Similar cases of heart failure in aortic aneurysm have been recorded by Rohr and Ryffel.[13]

In the three cases of valvular disease due to rheumatic fever there were pericardial adhesions as well as adhesions throughout the mediastinum. In these cases the clinical features were those of disease of the mitral valve and heart failure, and there was no good reason for believing that the pericardial adhesions were responsible for the heart failure. The venous congestion could have been caused by the heart failure and not by the compression of the veins by the mediastinal adhesions.

It is now admitted that the clinical features which have been described as being due to mediastinopericarditis can be reproduced by pericarditis alone (concretio cordis) in the absence of mediastinitis, since removal of the thickened pericardium is followed by complete recovery in some cases. It also seems clear that mediastinopericarditis may be associated with valvular heart disease, and in these cases it may be difficult to assess the relative importance of the valvular disease and the mediastinopericarditis in the production of the clinical picture. In some cases, at least, the valvular defects seem to dominate the picture, and the mediastinopericarditis is of little consequence so far as the symptoms and signs are concerned.

There are cases, however, in which both components of mediastinopericarditis are important, and these are generally cases of tuberculosis of the pericardium and mediastinum. For example, in the three cases of mediastinopericarditis described by Kussmaul[14] there was tuberculosis not only of the pericardium but of the mediastinum as well. In all the cases there were signs of circulatory failure and of hemorrhagic pulmonary infarction.

It seems plain, then, that chronic fibrous mediastinitis may in itself produce the signs of venous congestion in the tributaries of the superior vena cava, but when the signs of congestive heart failure are

13. Rohr, K., and Ryffel, W.: Ueber Einengungen und Verlegungen der Lugenschlagader durch Aortenaneurysmen, Frankfurt. Ztschr. f. Path. **36**:525, 1928.

14. Kussmaul, A.: Ueber schwielige Mediastino-Pericarditis und den paradoxen Puls, Berl. klin. Wchnschr. **10**:433, 445 and 461, 1873.

superimposed on this picture, the condition is due to involvement of the pericardium, compression of the pulmonary artery or an associated valvular disease. All these combinations may be observed. The involvement of both the pericardium and the mediastinum in cases of tuberculosis may explain in part the poor results of surgical treatment of tuberculosis of the pericardium when there is a clinical picture of concretio cordis.[15]

ABSCESS OF THE POSTERIOR MEDIASTINUM

Abscess in this region was more common than in the anterior space, the commonest causes being perforation of the esophagus and suppuration of lymph nodes. Other causes are extension of an infection from the retropharynx or from the spine. A rare cause is extension of infection from the lung, pleura or abdominal cavity.[16] This abscess shows only a slight tendency to approach the surface, but it extends up and down the posterior mediastinum. For this reason it may become large before producing symptoms of pressure. It may rupture into the bronchi, trachea, esophagus or pleural cavity. Rarely it may point in one of the posterior triangles of the neck, or it may extend retroperitoneally and point in the groin. The symptoms of an abscess of the posterior mediastinum may be indecisive, since a large accumulation of fluid can occur without producing many symptoms. The common ones are pain and dysphagia or irritative symptoms, such as cough and dyspnea.

The pain is felt most often on swallowing and coughing, but it is generally between the shoulder blades and may radiate anteriorly along the course of the intercostal nerves. When the trachea is encroached on it may be painful for the patient to perform any movements that involve the trachea, such as coughing or swallowing. Swallowing is also difficult, owing to compression of the esophagus, especially in the upper part of the chest.

The physical signs may be few, and the only ones found will be dulness over the spinal processes posteriorly and increase of whispered and spoken words. The most reliable signs are brought out by roentgenographic examination, which shows a rounded shadow with sharp borders and a convex outline on the lateral surface, extending from the midportion of the chest. The esophagus is displaced ventrally and laterally, and there is often obstruction to the flow of barium sulfate through it.

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15. Keefer, C. S.: Tuberculosis of the Pericardium: A Study of Twenty Cases, Ann. Int. Med. **10**:1085, 1937.

16. Auchinchloss, H., in discussion on Lambert and Berry.[2]

MEDIASTINAL ABSCESS FOLLOWING PERFORATION OF THE ESOPHAGUS

The commonest cause of posterior mediastinal abscess is perforation of the esophagus by a foreign body or a tumor. Rarer causes are compression necrosis from an aneurysm of the aorta or a tumor, rupture of the esophagus from vomiting [17] or dilatation of a stricture and perforation of a diverticulum.

From the standpoint of treatment, perforation of the esophagus is important. It is most often due to swallowing a bone of a fish or fowl or some other sharp-pointed body, such as a tack, nail or pin.

The following two cases illustrate the course of events when a favorable outcome follows a mediastinal abscess resulting from perforation of the esophagus by a foreign body.

CASE 3.—A young woman was admitted to the hospital complaining of swallowing a fish-bone, which was followed by pain in the upper part of the sternum and the left side of the back and by dysphagia. Examination showed nothing

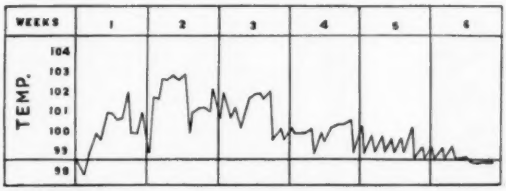

Fig. 2 (case 3).—Chart showing the temperature curve in a case of mediastinitis following perforation of the esophagus by a foreign body.

abnormal except that by fluoroscopic examination there was obstruction of the flow of barium in the upper part of the superior mediastinum.

The course of the illness was as follows: The temperature fluctuated, as shown in figure 2. During the first week the patient was extremely uncomfortable; the pain in the chest was severe, the temperature increased and the dysphagia and pain on swallowing increased. Roentgenographic examination showed an increased area of density in the superior mediastinum. On the seventh day of her illness she had an attack of retching which was followed by the vomiting of 6 ounces (175 cc.) of bright red blood and pus. After this she continued to regurgitate some blood and pus. On the twelfth day of illness she had another attack of vomiting, raising several ounces of blood, mucus and pus. The temperature remained elevated for three more weeks, but during this time she improved progressively. She continued to expectorate moderate amounts of pus for four weeks. This stopped during the fifth week, and during the sixth week the temperature became normal; she felt well, a roentgenogram of the chest was normal and she returned home completely recovered.

17. Weiss, S., and Mallory, G. K.: Lesions of the Cardiac Orifice of the Stomach Produced by Vomiting, J. A. M. A. **98**:1353 (April 16) 1932. Mallory, G. K., and Weiss, S.: Hemorrhages from Lacerations of the Cardiac Orifice of the Stomach Due to Vomiting, Am. J. M. Sc. **178**:506, 1929.

Summary.—A woman had a mediastinal abscess which developed after the swallowing of a fish-bone. Recovery followed the rupture of the abscess into the esophagus. The total duration of the illness was six weeks.

CASE 4.—A woman aged 44 years stated when admitted to the hospital that she had swallowed a fish-bone two weeks previously. While eating fish she felt that a bone became lodged in her throat, since she immediately had a choking sensation and a feeling of discomfort. Examination soon after this happened failed to reveal a foreign body, either by laryngoscopic or bronchoscopic study. The symptoms of a choking sensation, difficulty in breathing and coughing continued and were associated with dysphagia.

Examination.—When she was seen two weeks after the onset of her illness, she had fever, dysphagia, cough, with the expectoration of frothy sputum, and pain across the upper part of the right side of the chest anteriorly. Examination showed fever, tachycardia, leukocytosis (18,000 leukocytes) and signs of bron-

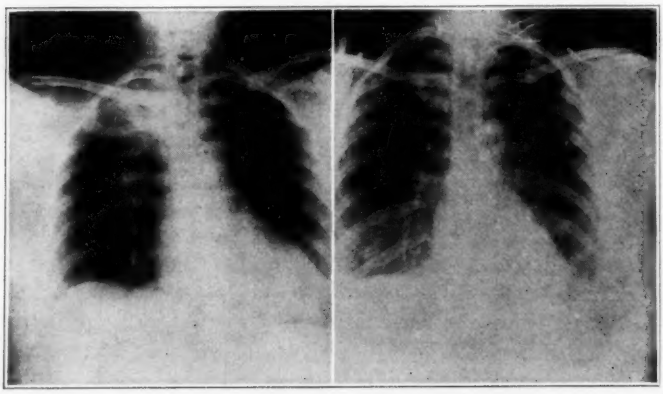

Fig. 3 (case 4).—Roentgenograms made in a case of mediastinitis caused by a pulmonary abscess due to a foreign body. The first roentgenogram was taken the first week of observation and shows the shadow in the upper mediastinum and the upper lobe of the right lung. The second one was taken after recovery.

chopneumonia of the right lung. The left lung was clear. There was increased retromanubrial dulness, especially to the right. Fluoroscopic examination showed a large dense shadow in the superior mediastinum at the level of the first and second ribs which did not pulsate but moved slightly on coughing, not on swallowing. It was situated about midway between the anterior and the posterior wall of the chest. There was no displacement of the esophagus, but the trachea seemed to be displaced slightly to the right. The temperature chart is shown in figure 3.

Course.—The patient's illness was of several months' duration, and during the first eight weeks of observation the course was as follows:

First Week: The patient had fever, tachycardia, cough and respiratory difficulty. There were many rales over the upper and lower lobes of the right lung. A roentgenogram showed a mass in the superior mediastinum and increased density of the upper lobe of the right lung as well as a triangular mediastinal

shadow extending to the right of the cardiac shadow. Moist rales were heard over the right lung posteriorly.

Second Week: The temperature remained elevated. The signs at the base of the right lung were diminishing, and a roentgenogram showed a diminution of the size of the shadow at the cardiophrenic angle. The shadow in the upper lobe of the right lung was also diminishing in size.

Third Week: The physical signs remained essentially the same as before, but a roentgenogram showed considerably more infiltration of the upper lobe and also of the lower lobe of the right lung. The cough increased in frequency and severity, the breath became foul and the sputum was more abundant and blood-streaked (fig 3).

Fourth Week: During this week the temperature was lower, and the rales over the lower lobe of the right lung diminished, but the coarse rhonchi and dulness over the upper lobe of the right lung persisted. A roentgenogram showed a great decrease in the density of the upper lobe of the right lung. The right cardiophrenic angle showed some haziness, and the right dome of the diaphragm was higher than the left dome.

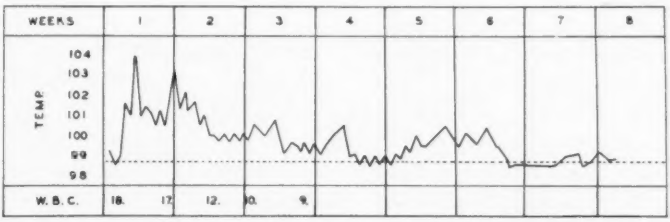

Fig. 4 (case 4).—Chart showing the temperature curve. The white blood cell counts are recorded in thousands per cubic millimeter.

Fifth and Sixth Weeks: Improvement continued, the signs in the lungs becoming fewer. Fluoroscopic examination at the beginning of the sixth week showed the trachea and esophagus pushed slightly to the left at the level of the first rib and some mottling of the apex of the right lung, with an increase in the linear markings extending from the pulmonary root toward the apex. The patient continued to complain of a foul breath, a bad taste and some pain in the right side of the chest, especially while lying on that side.

Seventh and Eighth Weeks: The patient continued to improve but had pain and distress over the upper part of the chest. A roentgenogram showed the esophagus in normal position and no signs of fistula or obstruction. There continued to be a shadow in the superior mediastinum which was abnormally large. At the end of this period she was allowed to return to her home. She remained there four weeks and then returned to the hospital.

Twelfth Week: For two weeks after leaving the hospital she felt greatly improved except for a continuation of the pain in the upper part of the right side of the chest anteriorly. Two weeks later the pain became more severe and spread across the upper part of the chest. It was a burning pain, often intermittent and not associated with cough or increased by respiratory effort. It was exaggerated when she was in a recumbent position. The examination revealed only diminished resonance over the upper lobe of the right lung. She was discharged again, after five days in the hospital.

First Year: One year after she swallowed the fish-bone she reported that after a violent attack of coughing, which had been precipitated by the inhalation of smoke, she coughed up a large fish-bone. After this she remained well.

Summary.—A woman swallowed a fish-bone, which caused a mediastinal abscess that perforated into the lung and drained. This healed entirely, and one year later, after a violent fit of coughing, the foreign body was dislodged. Complete recovery resulted.

This case illustrates what may happen after the perforation of the esophagus by a foreign body. There was evidence that the abscess had perforated the lung, producing pulmonary abscess, bronchopneumonia and physical signs. Roentgenographic examination indicated that the process was extensive also in the posterior mediastinum. It was striking that the signs of acute infection subsided after the healing of the pulmonary abscess and several months before the foreign body was recovered. This was an example of drainage of a mediastinal abscess after its rupture into the lung.

In addition to perforation of the esophagus by a foreign body, the most common cause is a neoplasm of the esophagus I [18] reviewed a group of these cases several years ago, including several in which mediastinitis was a feature.

A rarer form of suppurative mediastinitis arises from necrosis of the esophagus resulting from external pressure, especially that due to an aneurysm, a mediastinal tumor (usually a lymphosarcoma) or metastatic lymph nodes from the lung or esophagus. The following case illustrates the course in a case of mediastinal abscess due to erosion of the esophagus by an aneurysm:

Case 5.—A Negro aged 34 years complained of pain in the chest of one year's duration. Two weeks before admission to the hospital he had a severe constant boring pain in the chest, localized in the upper end of the sternum a few centimeters to the right of the midline. This was not exaggerated by respiratory effort, but it radiated into the middle of the back. It was constant day and night and prevented sleep. There was some cough, with expectoration of moderate amounts of sputum. He had syphilis fifteen years previously which had been treated inadequately.

The patient appeared uncomfortable. The temperature, pulse rate and respiratory rate were normal. The blood pressure was 150 systolic and 100 diastolic. There were a few rales at the base of the left lung posteriorly and a moderate increase in the retromanubrial dulness. The heart was of normal size, and the sounds were clear. The abdomen and extremities were normal. There was no anemia or leukocytosis; the Kahn and Hinton reactions were positive. Roentgenographic examination of the chest showed an enlarged aorta, an increase in the width of the mediastinal shadow and a fine mottling of the upper fields of both lungs, suggesting miliary tuberculosis (fig. 5).

18. Keefer, C. S.: Pleural and Pulmonary Complications of Carcinoma of the Esophagus, Ann. Int. Med. **8**:72, 1934.

The temperature varied from 98.6 to 100 F. for three days and then remained normal until death occurred. The pulse and respiratory rates gradually increased from 80 to 140 per minute and from 20 to 40 per minute, respectively. On the day after entrance to the hospital he became nauseated, and from that time on he regurgitated and vomited everything taken by mouth. The day before death (eight days later) he vomited small amounts of blood and had great respiratory distress, with both inspiratory and expiratory wheezing. The right lung showed many moist rales, but the left lung was clear. The respiratory difficulty increased, and he died on the ninth day.

Necropsy showed syphilitic aortitis with an aneurysmic formation in the descending arch which had ruptured into the mediastinum and the right pleural cavity. The blood clot in the mediastinum had eroded the esophagus and had

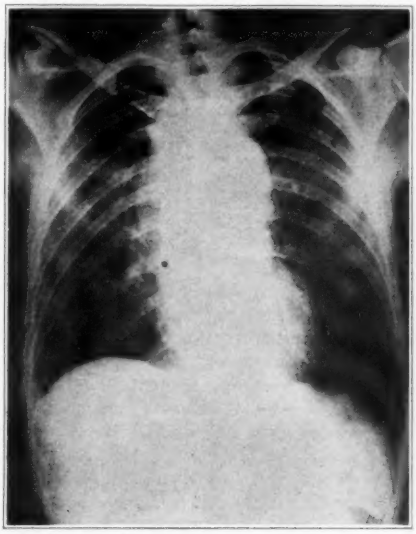

Fig. 5 (case 5).—Hematoma of the mediastinum following rupture of an aortic aneurysm.

caused perforation and a mediastinal abscess. The right bronchus was also compressed. There was, in addition, miliary tuberculosis of the lungs, liver, spleen and kidney, with caseous tuberculosis of both adrenal glands.

It is clear that this young man had an aneurysm of the aorta which bled into the mediastinum and the right pleural cavity. The blood clot had caused necrosis of the esophagus with perforation and an abscess of the mediastinum. There was chronic miliary tuberculosis without constitutional signs of infection. This case illustrates, then, how a mediastinal abscess can arise from a perforation of the esophagus from external pressure due to a hematoma. Similar cases of hematoma of

the mediastinum in aneurysm of the aorta have been recorded by Lenk [19] and myself.[18]

MEDIASTINAL ABSCESS FOLLOWING SUPPURATION OF LYMPH NODES

This condition is most important, since the prognosis seems to be better than in cases in which abscess in this area arises in some other way. The abscess may be due to hemolytic streptococci or pneumococcic infections and most often follows as infection of the throat, lungs or bronchi. An abscess arising from the throat is most often retroesophageal or peritracheal. The following two cases illustrate (1) the result of an infection arising in the throat and (2) an infection following an attack of grip:

CASE 6.—A man 46 years of age was admitted to the hospital on account of fever and sore throat. Five weeks previously he had an attack of coryza and tonsillitis which were not severe enough to confine him to bed. He continued with his daily work for two weeks, when he was forced to remain at home on account of chills, fever and difficult and painful swallowing. This was accompanied with attacks of coughing which was productive of mucopurulent sputum. During the third week of his illness the chills and fever continued, and the pain and difficulty in swallowing increased. In addition, he had some pain and discomfort about the base of the neck which radiated into the occiput during swallowing. The temperature gradually decreased, and he felt somewhat improved so far as the sore throat was concerned, but the dysphagia continued.

Physical Examination.—Physical examination showed that the patient was acutely ill and pale. He had few complaints, but it was difficult for him to swallow liquids or solid foods. The temperature was 101.5 F. The throat was red, and the pharynx seemed edematous and swollen. Palpation of the pharynx failed to reveal any localized mass, although the mucous membrane was swollen. The lymph nodes of the neck were not enlarged, and the thyroid gland was not palpable. The trachea was in the midline and could be moved laterally without discomfort; it moved up and down on swallowing, but this caused some discomfort. There was no swelling of the neck or area of tenderness on deep pressure. The movements of the cervical portion of the spine did not seem limited in extent. Examination of the chest failed to show any abnormal areas of prominence, and the superficial veins of the thoracic wall and the jugular veins were not swollen. There was no retromanubrial dulness or displacement of the heart or mediastinum laterally. The lungs were clear throughout. The heart was in normal position, and the sounds were clear. Dulness extended from the first to the fourth dorsal vertebra, and over this area the whispered voice and the breath sounds were distinct and bronchial. Aside from these abnormalities there was nothing distinctly abnormal to be made out on physical examination of the chest.

The abdomen was soft, and no organs were palpable. The extremities, genitalia and reflexes were normal.

Laboratory Examination.—The red blood cells numbered 3,860,000 per cubic millimeter, with 74 per cent (Sahli) hemoglobin. The white blood cells numbered 25,000 per cubic millimeter, with 85 per cent polymorphonuclear cells.

The urine was normal.

19. Lenk, R.: Die Röntgendiagnostik der intrathorakalen Tumoren und ihre Differentialdiagnose, Vienna, Julius Springer, 1929, p. 357.

Roentgenographic examination showed the heart in normal position; the pulmonary fields were clear. In the superior mediastinum there was a bilateral rounded shadow with concave borders, slightly more prominent on the right side than the left. It was distinctly supra-aortic, and it had not displaced the trachea laterally or the aortic arch downward (fig. 6).

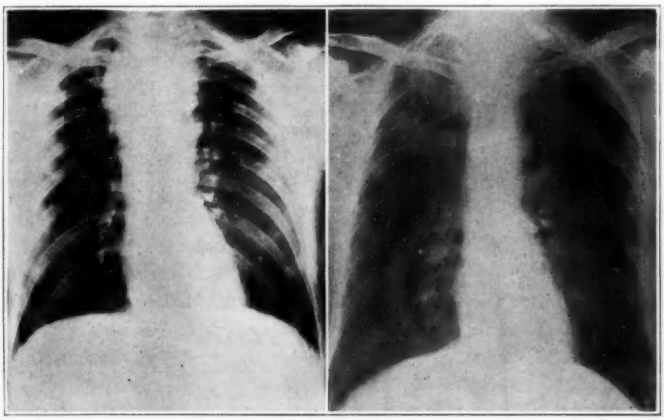

Fig. 6 (case 6).—Mediastinitis. The first roentgenogram indicates the condition on the third day of observation, four days before operation. The abscess is seen in the supracardiac area. The aorta is not displaced downward. The shadow is in the posterior mediastinum and projects more to the right than to the left. The second roentgenogram was taken six weeks after the operation. The mediastinum is clear. The defect in the ribs following operation is visible.

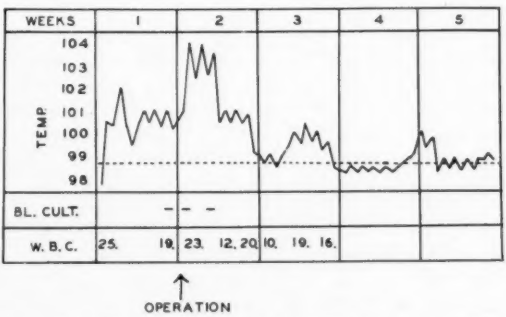

Fig. 7 (case 6).—Chart showing the temperature curve. The white blood cell counts are recorded in thousands per cubic millimeter.

Fluoroscopic examination showed that this shadow was retroesophageal and in the posterior mediastinum. The esophagus was displaced ventrally and slightly to the left. As the barium entered the esophagus it paused momentarily at this area before passing downward.

Course of the Illness.—A chart of the temperature is shown in figure 7. On the seventh day of hospitalization the patient was operated on by Dr. Irving J. Walker. The posterior mediastinum was opened, a portion of the second, third and fourth ribs was resected close to their articulation with the spine, an abscess containing 300 cc. of thin purulent material was opened and a drain was inserted. The pleura was not entered.

After the operation there was an increase in the temperature for several days, but it gradually subsided and returned to normal within twenty-one days. The pus from the abscess showed a pure culture of streptococci, and the drainage was profuse for several weeks. Because of anemia he was given two blood transfusions, and he improved considerably. After several months the cavity gradually diminished so that little drainage was evident. He gained weight and felt greatly improved. When he was seen two months after the operation, he appeared well and had returned to work. There was only a small draining sinus in the back.

In the present case it seems likely that the infection of the posterior mediastinum resulted from an extension of the infective process in the pharynx to the retrovisceral space. The other possibility, of course, is that the abscess arose from suppurating lymph nodes in the posterior mediastinum. This type of infection has been studied extensively by Lerche,[1] who has emphasized the importance of infections of the mediastinal lymph nodes in the causation of mediastinitis. They are analogous to infections of the retropharyngeal lymph nodes with abscess formation in children, the main difference being in the location of the infection.

MEDIASTINAL ABSCESS FOLLOWING INFECTION OF THE RESPIRATORY TRACT

CASE 7.—A man aged 25 years complained of pain in the chest and difficulty in swallowing. He had been well until two weeks before admission to the hospital, when he had an illness that was characterized by malaise, generalized aches and pains, and fever. These symptoms soon disappeared, and he felt improved for several days. Then substernal pain on swallowing developed. This pain grew worse, and fever was present. Gradually the pain became more diffuse and could be felt in the region of the ensiform process of the sternum. He then began to have severe pain in the front of the chest that radiated to the back between the shoulder blades. The severe pain lasted five days, and during this time he had a feeling of heaviness and difficulty in swallowing. He could not eat solid food, and he stated that he felt as though there were a mass in the upper part of the chest.

Physical Examination.—When he was seen, ten days after the onset of his illness, he complained of fever, pain in the chest and dysphagia. The temperature was 102 F., and he appeared acutely ill. Physical examination showed increased redness of the pharynx and increased dulness to percussion over the spine posteriorly; otherwise it revealed essentially no abnormality.

Laboratory Examination.—The white blood cell count was 25,000 per cubic millimeter. A roentgenogram of the chest showed an increase in the width of the shadow in the superior mediastinum, but the lungs were clear.

Course of the Illness.—The temperature is charted in figure 8. For the first three days of hospitalization the patient felt somewhat improved, in that the substernal pain was less severe, but the difficulty in swallowing persisted. On the third day there was dulness over the upper lobe of the right lung posteriorly, and numerous rales were heard. On the sixth day he had an attack of coughing and raised half a cupful of blood-streaked material which showed pure culture of hemolytic streptococci. The difficulty in swallowing was slightly relieved, but regurgitation of food and fluid occurred occasionally. A roentgenogram of the chest showed density in the upper lobe of the right lung, and numerous rales were heard over this area. Eight days after the attack of coughing the temperature returned to normal, the signs in the chest gradually subsided, the dysphagia became less, the white blood cell count became normal and he left the hospital, after being there twenty-eight days. He felt well except for slight difficulty in swallowing solid foods. This subsided within two weeks, and he has remained well.

The important features of this case were the attack of grip two weeks before the patient's admission to the hospital and the onset of acute symptoms suggesting a mediastinal abscess, such as substernal pain, painful and difficult swallowing and an increase in the supracardiac

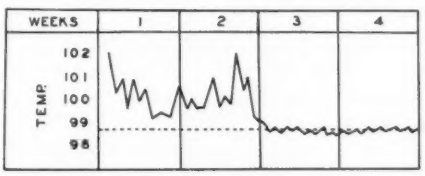

Fig. 8 (case 7).—Chart showing the temperature curve for a patient with postinfluenzal mediastinitis. The febrile reaction was of two weeks' duration.

roentgenographic shadow. He finally recovered after the expectoration of the contents of an abscess which had evidently perforated the lung or a bronchus. Hemolytic streptococci were recovered from the expectorated material.

Similar abscesses of the mediastinum following suppuration of lymph nodes have been reported by Lerche,[1] Richards,[20] Malnekoff,[21] Farnum,[22] Lambert and Berry,[2] Fischer,[23] Neuhof,[24] and others. These cases are so important as to require special comment. In a few cases the symptoms and signs of mediastinal abscess followed an infection of the respiratory tract which had not been severe or disabling. Lerche [1]

20. Richards, L. G.: Peritracheal Abscess, Tr. Am. Bronch. Soc. **12**:71, 1929.

21. Malnekoff, B. S.: Acute Mediastinal Abscess, Am. J. Dis. Child. **39**:591 (March) 1930.

22. Farnum, W. B.: Acute Suppuration of the Mediastinum, New York State J. Med. **35**:724, 1935.

23. Fischer, R. C.: Abscess of Mediastinum, J. Thoracic Surg. **6**:212, 1936.

24. Neuhof, H.: Acute Infection of Mediastinum, J. Thoracic Surg. **6**:184, 1936.

recorded cases in which the abscess appeared, or at least was discovered, three years after an attack of influenza or pneumonia. In several cases recovery followed the expectoration of material contained in the abscess. In one instance the abscess perforated the lung and the esophagus. The history in these cases is of influenza with pneumonia or of influenza followed by cough and frequent colds and after an indeterminate period by pain, dysphagia, cough and dyspnea. Roentgenograms show a shadow in the posterior mediastinum, and there are symptoms and signs of infection. Unless the abscess is drained or aspirated, it often ruptures into the lung, bronchus or esophagus, and in this way recovery may take place, or death may follow from widespread infection. Occasionally empyema arises and obscures the diagnosis, and atelectasis from bronchial pressure has been observed.

It is well to recall, then, that fever and thoracic symptoms following influenza, attacks of pneumonia or sore throat may be due to an abscess in the posterior mediastinum.

CHRONIC ABSCESS OF THE POSTERIOR MEDIASTINUM

A chronic abscess of the posterior mediastinum is almost always due to tuberculosis arising from the vertebrae or from caseous lymph nodes. Other causes for such an abscess are actinomycosis and pyogenic infections of the vertebrae or lymph nodes. This abscess occurs most often in the lower cervical and upper dorsal regions and commonly forms a circumscribed mass that is confused with a solid tumor. It gravitates downward from the point of origin and may appear in the abdominal wall or in the regions where a psoas abscess perforates. Rarely such an abscess perforates a bronchus. Infrequently there is diffuse mediastinitis instead of an abscess, and I have observed tuberculous pleuritis after extension of an infection from the spine to the pleura.

The symptoms are due to the primary lesion and to the presence of the space-occupying process in the mediastinum. Fever, pain in the back, dysphagia, cough and gradual wasting are common complaints. The physical signs depend on the size of the abscess and its origin. There is tenderness over the spine in many cases when the vertebrae are the source of the abscess, but in some cases the focus of necrosis in the spine is so small that this sign will be missing. There may be dulness over the upper part of the spine and increase of the whispered voice, indicating a lesion in the posterior mediastinum.

The most important signs are those revealed roentgenographically. This examination should include an anteroposterior and a lateral view of the mediastinum and spine. The shadow cast by the abscess may be in the superior mediastinum or superimposed on the cardiac shadow. There may or may not be demonstrable erosion of the vertebrae.

The shadow is homogeneous, with a sharp convex border. It is almost invariably symmetric and bilateral. It is situated in front of the spine and behind the esophagus, and its axis is parallel with the long axis of the body. It is seen best in the middle or lower part of the posterior mediastinum, it is superimposed on the cardiac shadow and it pushes the esophagus forward.

In general, then, a diagnosis of tuberculous abscess may be made in the presence of low grade fever, pain due to pressure on a nerve and destruction of bone, symptoms of compression of organs, such as the esophagus or bronchi, and roentgenographic changes.

The following two cases illustrate the course of events in tuberculosis of the posterior mediastinum:

Case 8.—A 20 year old girl was first seen in January 1931, complaining of excessive fatigue, dyspnea and slight edema of the ankles of several years' duration. She stated that she had rheumatic fever a number of years previously and that two months before her admission to the hospital a mass of tender red nodules developed over the legs and lasted five weeks. These finally disappeared, and the only abnormality that was found on physical examination at the time of entry was slight enlargement of the heart, with a systolic murmur. There was no fever. The white blood cell count was 6,800 and the hemoglobin value 95 per cent. A roentgenogram of the chest showed a dense area on the right side of the superior mediastinum which did not pulsate when examined by fluoroscopy. An electrocardiogram was normal. The diagnosis at that time was rheumatic heart disease with mitral regurgitation and a mediastinal tumor of unknown etiology. She was discharged from the hospital and followed for several weeks before being readmitted for further examination. For three weeks after her first discharge from the hospital she felt reasonably well; then she began to have fever, chilly sensations, and pain and swelling of the wrists, hands and joints, which seemed to occur after a sore throat. When she reentered the hospital she had a fever and leukocytosis (15,600 leukocytes). A roentgenogram of the chest showed evidence of a mass to the right of the sternum in the superior mediastinum. The heart was moderately enlarged. Electrocardiographic examination showed preponderance of the left ventricle. On more careful questioning it was found that after a sore throat her hands and wrists began to swell and were painful and tender to touch. The entire left arm was likewise painful. There was some stiffness of the left shoulder. After about three days of pain and discomfort the articular symptoms subsided. Four days before entry she had a cough and some soreness in the right side of the chest. There was no sputum. She felt prostrated and chilly and had interrupted sleep. She would awake during the night and drink large quantities of water.

It was thought that the patient had subacute rheumatic fever which followed erythema nodosum and that the cardiac lesion was due to mitral regurgitation. The question of subacute bacterial endocarditis was raised. Culture of the blood made on the day of her admission to the hospital was sterile.

Course of the Illness.—For eleven months, while she was observed, there was an irregular fever, the temperature varying daily from 99 to 101 or 102 F. and sometimes to 104 F. There was a corresponding elevation of the pulse rate; it varied between 100 and 120 beats per minute. The respiratory rate was normal. Repeated roentgenograms of the chest showed a mass in the superior mediastinum.

It did not pulsate and was considered for some time to be due to Hodgkin's disease. For that reason she was subjected on several occasions to high voltage roentgen therapy over the chest. As the disease progressed, this shadow seemed to diminish somewhat in size, but later it seemed to increase in the lower half of the chest near the mediastinum. On one occasion the patient complained of pain on the right side of the manubrium; there was excruiating tenderness over this area. There was no swelling or pulsation. Nine of the ten blood cultures taken at different intervals during the course of the disease were sterile; one showed a few green streptococci. This finding was never confirmed.

One month after the patient was admitted to the hospital she began to complain of small tender lumps on the back of the chest. These nodules appeared over the tibia, hands and the back. They were well circumscribed, painful and tender to touch. A diagnosis of erythema nodosum was made. These nodules kept recurring from time to time for five months. Some of them broke down and were seen to contain a thick purulent material which was sterile on culture.

Four months before death, signs developed which were interpreted as due to pneumonia of the base of the right lung. There was no cough or expectoration at the time, and after a week or ten days these signs gradually diminished. There was no essential change in the condition until three weeks before death, when she began to notice an increase in the swelling and tenderness of the knee joints. This continued, and the left ankle became swollen. She failed gradually and died eleven months after admission to the hospital.

Laboratory Examination.—Electrocardiographic examination showed sinoauricular tachycardia, a PR interval of 0.12 second, a QRS complex of 0.06 second, an upright T wave in leads I and II, an inverted T wave in lead III, preponderance of the left ventricle, but no other changes or abnormalities. The white blood cell count varied from 6,000 to 16,200, the average count being between 5,000 and 8,000 per cubic millimeter. The polymorphonuclear count varied between 80 and 90 per cent and the lymphocyte count between 8 and 16 per cent; the monocyte count was 2 per cent. No abnormal cells were found. The red blood cell count, which was normal on entering, gradually declined to 3,960,000, when the hemoglobin value was 58 per cent. Anemia, however, was not an outstanding feature of her illness. Agglutination tests for undulant fever gave negative results.

Necropsy.—Necropsy revealed a mediastinal abscess which had extended into the right pleural cavity and had invaded the eleventh rib, causing interlobar pleurisy. In addition, there was synovitis of both knee joints and the left ankle joint. Microscopic examination showed all these lesions to be due to tuberculosis.

CASE 9.—A 20 year old woman was seen for the first time in January 1932, when she complained of pain in the chest, a tired feeling and loss of weight and of appetite of six months' duration. She had previously always been well and healthy. At the age of 17 she married and had two healthy children. The second child was born fourteen months before the patient was seen. There was nothing abnormal about the pregnancy or delivery. She felt well until six months before entry, when she began to notice excessive fatigability and progressive loss of weight and appetite. She consulted her physician, who studied her by means of fluoroscopy and roentgenograms, but nothing definite was found to account for her symptoms.

Four months after the onset of her illness a productive cough developed. The sputum was yellowish and was said to amount to about half a pint daily. On one occasion she raised a small amount of blood-streaked sputum, but after several

weeks the cough and sputum subsided completely. For five weeks before admission to the hospital she remained in bed. During this time she felt hot and had night sweats and insomnia. Her temperature in the afternoon fluctuated between 99 and 101.4 F. She complained of some pain in the thorax and arms, especially the shoulders and elbow joints. Her neck had been stiff for about a month.

Physical Examination.—The patient had obviously lost a considerable amount of weight. Her complexion was fair and her skin pale. There was no cyanosis. A careful examination failed to reveal anything abnormal except slight stiffness of the neck in flexion and extension and moderate enlargement of the thryoid gland. There were no physical signs of abnormality of the lungs or heart. The temperature was 100.6 F., the pulse rate 100 and the respiratory rate 20 per minute.

Laboratory Examination.—The urine was normal. A blood count showed: red blood cells, 4,380,000 per cubic millimeter; hemoglobin, 67 per cent, and white blood cells, 10,000 per cubic millimeter, with 56 per cent polymorphonuclears, 37

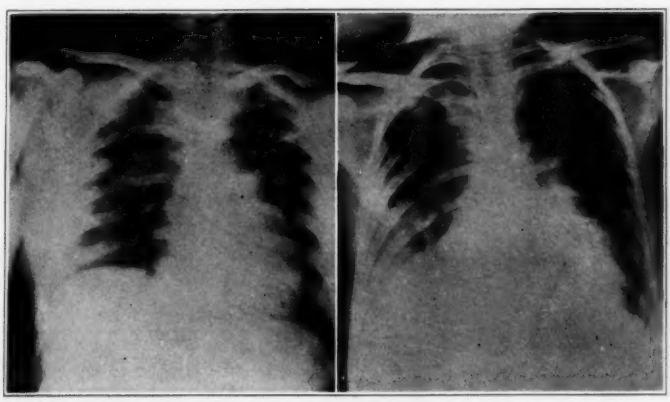

Fig. 9 (case 8).—Posterior mediastinitis due to tuberculosis. The first roentgenogram shows a shadow in the upper mediastinum during the third week of observation; the second indicates the mediastinal and pulmonary lesions during the forty-fourth week of illness.

per cent lymphocytes, 3 per cent monocytes, 1.5 per cent eosinophils and 1.5 per cent basophils. The stained smear appeared normal. The sedimentation rate was increased over normal. Culture of the blood was sterile, and the stool was normal. The basal metabolic rate was plus 3 per cent. The reaction to the tuberculin test (1:100) was positive. The nonprotein nitrogen content of the blood was 19 mg. per hundred cubic centimeter. Numerous roentgenograms of the chest, mediastinum and cervical portion of the spine were made. The lungs were within normal limits. The cervical portion of the spine showed a thickening of the musculature anterior to the spine, with displacement of the trachea forward. A thick barium meal showed that the esophagus was displaced forward and slightly to the left by a symmetric mass which cast a triangular shadow in the lower cervical and upper thoracic portions of the spine. The cervical portion of the spine appeared normal.

Course of the Illness.—The patient was under observation for three months. For the first five weeks of observation her temperature ranged daily from 99 to 100.5 or 101 F. When she left the hospital her temperature ranged between normal and 99.6 F. in the afternoon. Her weight increased from 89 to 112 pounds (51 Kg.) during the three months.

Numerous examinations of the blood failed to show any alteration in the white blood cells. The total count varied between 7,500 and 10,000 per cubic millimeter. The hemoglobin value increased while the patient was under observation from 67 to 85 per cent, and the red blood cell count increased from 4,380,000 to 5,380,000 per cubic millimeter. It was not possible to obtain any sputum for examination, and tuberculosis was never proved as far as infection of the lung was concerned. She left the hospital, returned to her home and was not seen for three years.

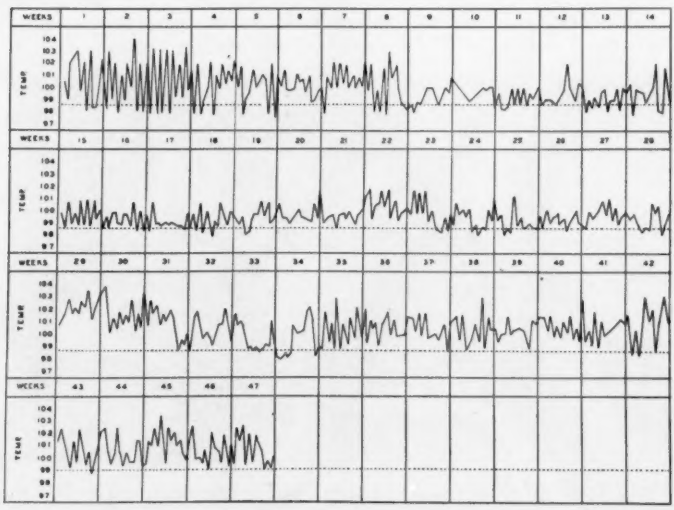

Fig. 10 (case 8).—Chart showing the temperature curve.

After her discharge from the hospital, in 1932, she remained well, gained weight and had no complaints until the autumn of 1934, when she began to notice malaise, fatigability and fever, with anorexia and progressive loss of weight. After these symptoms continued for several months a new symptom appeared—dysphagia, with a choking sensation in the throat which provoked an unproductive cough. These symptoms continued unabated until she returned to the hospital in February 1935, when she complained of recurrent headaches and severe pain in the neck and spine of several months' duration.

The examination in 1935 showed that the patient was uncomfortable. The face was flushed, and she had obviously lost a considerable amount of weight. The temperature was elevated above normal; the pulse and respiratory rates were increased. Examination revealed tenderness over the seventh cervical and the first dorsal vertebra. The lungs were clear, and the heart, abdomen and extremities were normal. The blood showed evidence of hypochromic anemia. The sedi-

mentation rate was increased, the reaction to the tuberculin test was positive and agglutination tests for Bacillus typhosus, Bacillus paratyphosus and Bacillus melitensis gave a negative reaction. Roentgenograms of the chest are shown in figure 12. The conspicuous feature was the bilateral shadow in the posterior and in the superior mediastinum, with a sharp, well defined border, broader in its cephalic portion. Anterior and lateral views of the cervical portion of the spine were normal. An incidental finding was bilateral cervical rib. The mass was retrotracheal and had displaced the trachea anteriorly; the esophagus was displaced anteriorly and to the left of the midline.

The record of the temperature is shown in figure 11. It is noticeable that there was irregular fever for eighteen weeks. During this time the patient lost weight and strength. The physical findings so far as the chest was concerned did not change. Gradually the temperature became lower. She entered a sanatorium for tuberculous patients for further treatment and remained for six months. During this time she improved continually, gaining weight and strength,

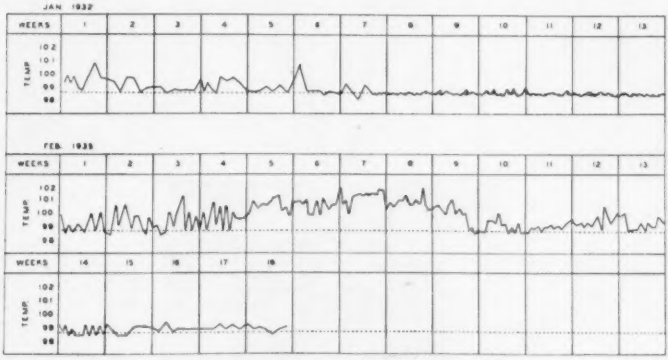

Fig. 11 (case 9).—Chart showing the temperature curves for a patient with mediastinitis due to tuberculosis during two periods of hospitalization.

her temperature remained normal and she returned home after rest and general upbuilding.

After leaving the sanatorium she remained well and when seen in 1937 had no complaints. Roentgenograms failed to show any change in the spine, and the shadow in the mediastinum which had been present in 1932 and 1935 had disappeared completely.

Summary.—A young woman, who was followed for over five years, had two prolonged bouts of fever without leukocytosis but with signs of an abscess in the mediastinum which was probably tuberculous in origin. This was present in spite of the fact that no signs of Pott's disease could ever be elicited. Recovery followed conservative treatment.

While the precise etiologic diagnosis was not made in this case, the repeated attacks of fever, the chronicity and the location of the infective process and the strongly positive reaction to the tuberculin test were all in favor of tuberculosis. This case serves to illustrate that a tuberculous abscess may be located in the posterior mediastinum with-

out a roentgenographically demonstrable lesion in the spine. Failure to demonstrate such a lesion roentgenographically does not exclude this focus. Heuer has recorded a case in which an abscess of the posterior

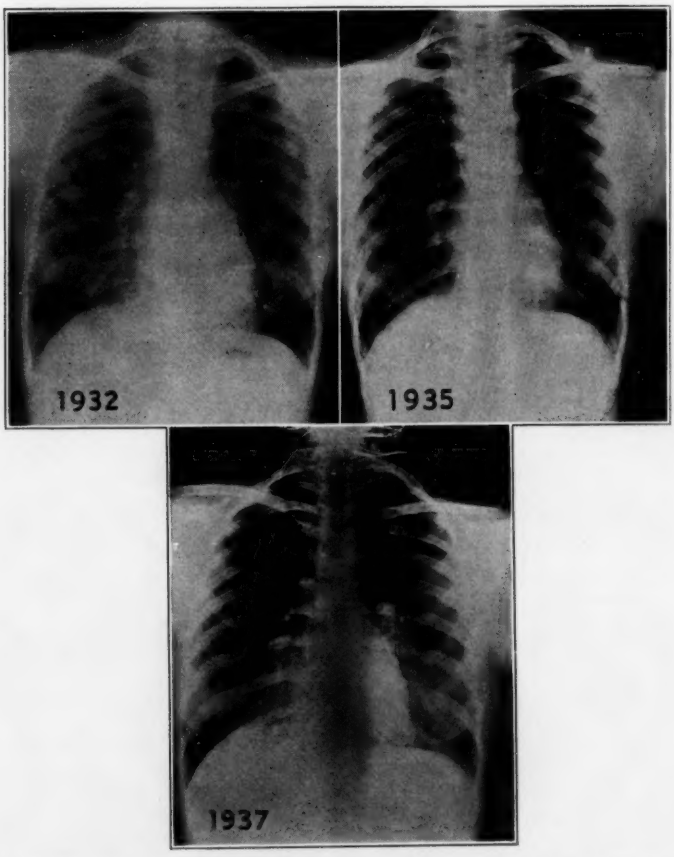

Fig. 12 (case 9).—The roentgenograms taken in 1932 and 1935 show an abscess in the posterior mediastinum. By 1937 it had disappeared.

mediastinum followed caries of the spine; it was not possible to demonstrate the area of necrosis in the vertebrae roentgenographically, but it was present at the time of operation. It is also impressive that such an abscess can resolve spontaneously with conservative treatment.

MEDIASTINITIS FOLLOWING PNEUMONIA

During the pandemic of influenza in 1918 numerous cases of mediastinitis due to hemolytic streptococci [25] were reported, and it was repeatedly pointed out that the mediastinal lymph nodes in fatal cases were swollen and suppurating. This diffuse infection of the mediastinum was always a serious complication, as the following case illustrates:

CASE 10.—A young man was admitted to the hospital with lobar pneumonia due to type I pneumococci with bacteremia. In spite of the administration of large amounts of antipneumococcus horse serum, his temperature did not return to normal. It was then found that he had a mixed infection, since the sputum contained large numbers of hemolytic streptococci as well as pneumococci. On the eleventh day of his illness there were signs of mediastinopericarditis, with a loud friction rub which was synchronous with the heart beat and which was exaggerated by respiration. On the thirteenth day hoarseness developed, and he

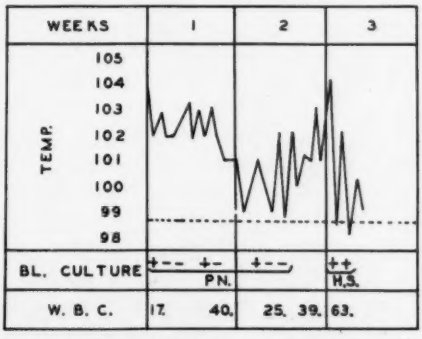

Fig. 13 (case 10).—Chart showing the temperature curve in a case of mediastinitis following pneumonia. The first three cultures of the blood showed type 1 pneumococci; the last two, hemolytic streptococci. The white blood cell count is recorded in thousands per cubic millimeter.

was unable to speak above a whisper; the following day he had pain under the gladiolus and difficulty in swallowing. He died on the seventeenth day of his illness. The results of culture of the blood, the white blood cell counts and the temperature chart are shown in figure 13.

The necropsy showed resolving pneumonia on the right side, with many abscesses of the lung, diffuse mediastinitis and empyema (hemolytic streptococci) on the right side in the anterior mediastinal pleural space.

This case emphasizes two points: first, the seriousness of mediastinitis in lobar pneumonia and, second, the importance of mixed infections in this disease, a feature that has been studied and reviewed most thoroughly by Finland,[26] Parsons and Myers [27] and Solomon and

25. Farnum.[22] Fischer.[23]

26. Finland, M.: The Significance of Mixed Infections in Pneumococcic Pneumonia, J. A. M. A. **103**:1681 (Dec. 1) 1934.

27. Parsons, J. W., and Myers, W. K.: Streptococcic Sepsis Complicating Recovery from Pneumococcic Pneumonia, J. A. M. A. **100**:1857 (June 10) 1933.

Curphey.[28] It also emphasies the importance of substernal pain and dysphagia in the diagnosis of mediastinitis.

COMMENT

The cases reported in this paper illustrate that an acute abscess or a chronic inflammatory lesion of the mediastinum may occur as a result of a variety of infections. In some cases the process is only part of a more widespread and extensive process, and for that reason it is of interest only so far as the complete diagnosis is concerned. In other cases, however, an abscess is the principal lesion, and when recognized it can be treated with a reasonable degree of success. For this reason it is necessary to recognize the conditions which cause mediastinal abscess and to be familiar with the features in these cases.

SUMMARY AND CONCLUSIONS

From a study of sixty cases of acute and of chronic mediastinitis the following conclusions are justified:

Acute and chronic mediastinal infections are most common in the posterior mediastinum.

The common causes of posterior mediastinitis are perforation of the esophagus and suppurative lymph nodes. Other causes are lesions in the spine, lungs, pleura and abdomen. Infections due to tubercle bacilli or hemolytic streptococci are frequent causes.

Abscess of the anterior mediastinum results most often from an infection in the neck or from osteomyelitis of the sternum. A chronic infection in this location is usually due to tuberculosis or syphilis.

The diagnosis of mediastinal abscess depends on: (1) the presence of a condition which is capable of producing mediastinal infection, (2) the symptoms and signs of an infection, with local physical signs referable to the mediastinum, and (3) the results of aspiration or exploration.

On the whole, the prognosis in mediastinal abscess is poor, largely because of the presence of the process that is responsible for the abscess. When the process is localized to a part of the mediastinum which is accessible for surgical treatment, the prognosis is better.

Chronic fibrous mediastinitis is due to healed or active tuberculosis, syphilis or pyogenic infection. There is often an associated fibrous pericarditis, so that the clinical picture may be that of congestive heart failure due to cardiac compression.

Cardiac failure with congestion may also accompany mediastinitis when there is an associated defect of the mitral valve or an aneurysm of the aorta compressing the pulmonary artery. When this is the case the mediastinitis may be latent or may play only a small part in the clinical features.

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28. Solomon, S., and Curphey, T. J.: Streptococcic Septicemia Complicating Pneumococcic Lobar Pneumonia, J. A. M. A. **108**:187 (Jan. 16) 1937.

INFLUENCE OF DIARRHEA ON THE VITAMIN B_1 REQUIREMENT

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AND
GEORGE R. COWGILL, PH.D.
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Chronic diarrhea occurs as a symptom in a great variety of diseases (table 1). In the management of the majority of these conditions, one of the problems of prime importance is the assurance of an adequate supply of dietary essentials. Without intending to minimize the importance of mineral constituents or of the other substances known to be necessary in the diet, we present this study concerned with one particular aspect of the problem, namely, the amount of vitamin B_1 which may be required by patients suffering from diarrhea.

The literature contains abundant clinical evidence that disorders due to dietary deficiencies, usually multiple but particularly of the vitamins of the B complex, occur as complications of chronic diseases of the alimentary tract. Signs and symptoms of pellagra and beriberi have been observed in carcinoma of the gastrointestinal tract (Rolph,[1] 1916; Eusterman and O'Leary,[2] 1931), in ulcerative colitis (Barnes,[3] 1926; Mackie,[4] 1935) and after short-circuiting operations on the intestines

This project was aided by a grant from General Mills, Inc.

From the Laboratory of Physiological Chemistry, Yale University School of Medicine.

Throughout this paper the term milligram equivalent is used to indicate 0.05 U. S. P. unit (Cowgill, G. R.: The Vitamin B Requirement of Man, New Haven, Conn., Yale University Press, 1934.

* Fellow of the Henry Strong Denison Foundation for Medical Research, 1934-1935. The data presented in this article are from a thesis submitted to the faculty of the Yale University School of Medicine in partial fulfilment of the requirements for the degree of Doctor of Medicine.

1. Rolph, F. W.: Cancer of the Stomach and Pellagra in the Same Patient, Canad. M. A. J. **6**:323-324 (April) 1916.

2. Eusterman, G. B., and O'Leary, P. A.: Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastrointestinal Tract, Arch. Int. Med. **47**:633-649 (April) 1931.

3. Barnes, J. M.: Typical Pellagra Syndrome Developing in Patient with Chronic Ulcerative Colitis While Under Hospital Treatment, Ann. Clin. Med. **4**:552-564 (Jan.) 1926.

4. Mackie, T. T.: Ulcerative Colitis: II. The Factor of Deficiency States, J. A. M. A. **104**:175-178 (Jan. 19) 1935.

(Jones,[5] 1933; Urmy, Ragle, Allen and Jones,[6] 1934). In the treatment of patients with chronic diarrheal conditions, particularly ulcerative colitis, Larimore[7] (1928), Bargen and Victor[8] (1931) and others have advocated the administration of diets rich in vitamins, especially vitamin B. Bargen and Victor have recommended the addition of 200 mg. of brewers' yeast daily to the bland diet usually tolerated by these patients.

In the treatment of bacillary dysentery the value of "vitamin preparations given with a definite purpose in view and not haphazard" has been mentioned by Corner[9] (1935), and the specific value of parenteral administration of vitamin B_1 in a form of infantile diarrhea prevalent in Palestine has been described by Grünfelder and his colleagues[10]

TABLE 1.—*Classification of Etiologic Factors in Chronic Diarrheas* *

I. Infectious and parasitic diseases	VI. Allergic disorders
Bacillary dysenteries	VII. Chronic passive congestion
Amebic dysentery	Cardiac failure
Tuberculosis of the gastrointestinal tract	Cirrhosis of liver
Diseases due to other organisms	VIII. Operative procedures
II. Toxic disorders	Intestinal resection
Poisoning due to mercury, arsenic, etc.	Malfunctioning gastroenterostomy
Uremia	IX. Gastrogenic disorders
III. Endocrine disorders	Achylia
Addison's disease	Delayed emptying
Thyrotoxicosis	X. Irritative disorders
IV. Neoplasms	Fermentative and putrefactive conditions
V. Deficiency states	XI. Neurogenic and psychogenic disorders
Beriberi	XII. Disorders of unknown etiology
Sprue	Ulcerative colitis
Pellagra	Regional ileitis

* Modified from classifications published by H. W. Bettman (Diarrhea, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1934, vol. 5, pp. 355-364), J. L. Kantor (Treatment of Common Disorders of Digestion, ed. 2, St. Louis, C. V. Mosby Company, 1929, p. 242; Diarrhea, Am. J. Digest. Dis. & Nutrition **2**:1-7 [March] 1935) and P. W. Brown (Diagnosis and Treatment of Certain Types of Chronic Diarrhea, Ann. Int. Med. **8**:93-99 [July] 1934).

5. Jones, C. M.: Peripheral Complications of Ulcerative Colitis, M. Clin. North America **16**:919-928 (Jan.) 1933.

6. Urmy, T. V.; Ragle, B. H.; Allen, A. W., and Jones, C. M.: Beriberi Secondary to Short-Circuited Small Intestine, New England J. Med. **210**:251-254 (Feb. 1) 1934.

7. Larimore, J. W.: Chronic Ulcerative Colitis: Observations of Treatment by Diet, Tr. Am. Gastro-Enterol. A. **30**:298-318, 1928.

8. Bargen, J. A., and Victor, M.: Diet in Intestinal Disorders, J. A. M. A. **97**:151-154 (July 18) 1931.

9. Corner, H. W.: Bacillary Dysentery: A Summary of Treatment, Brit. M. J. **1**:1162-1165 (June 8) 1935.

10. Grünfelder, B.; Rabinovici, E.; Geiger, A., and Rosenberg, A.: Ueber die therapeutische Wirkung von intravenös verabreichtem B_1-Vitamin in der Behandlung der Ernährungsstörungen mit toxischen Erscheinungen bei Säuglingen, Klin. Wchnschr. **12**:983-985 (June 24) 1933.

(1933). The controversy as to whether vitamin therapy is of any avail in intestinal tuberculosis, illustrated by the reports of McConkey [11] (1930) and of Steinbach and Rosenblatt [12] (1935) pro and con, respectively, may be due in part to the fact that in the administration of vitamins physicians have had little information as to how much of each vitamin is actually needed by the patient.

Few data have been available on which to base quantitative prescriptions. In the present investigation an approach to the problem has been made by determinations of the effect of diarrhea on the vitamin B_1 requirement of dogs under various conditions. The clinical value of such experiments depends, first, on the accuracy of the methods used and, second, on the applicability of the results to human beings. An accurate determination of the individual animal's requirement for vitamin B_1 under any desired conditions has been made possible and relatively easy by a standardized method that has been devised (Cowgill, Deuel and Smith,[13] 1925) to utilize the appearance of the specific anorexia which develops as an early sign of deficiency of this dietary essential. After the development of this method and the determination of the normal requirement of the dog, we undertook an extensive research project to discover the influence on the vitamin B_1 requirement under a number of conditions, including exercise (Cowgill, Rosenberg and Rogoff,[14] 1931), disease of the thyroid gland (Himwich, Goldfarb and Cowgill,[15] 1932), fever (Cowgill and Dann,[16] 1936) and diuresis (Cowgill, Rosenberg and Rogoff,[17] 1930). The present study is a part of this series of experiments.

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11. McConkey, M.: The Treatment of Intestinal Tuberculosis with Cod Liver Oil and Tomato Juice, Am. Rev. Tuberc. **21**:627-635 (May) 1930.

12. Steinbach, M. M., and Rosenblatt, M. B.: Vitamin Therapy in Intestinal Tuberculosis, Am. Rev. Tuberc. **31**:35-43 (Jan.) 1935.

13. Cowgill, G. R.; Deuel, H. J., Jr., and Smith, A. H.: Studies in the Physiology of Vitamins: III. Quantitative Aspects of the Relation Between Vitamin B and Appetite in the Dog, Am. J. Physiol. **73**:106-126 (June) 1925.

14. Cowgill, G. R.; Rosenberg, H. A., and Rogoff, J.: Studies in the Physiology of Vitamins: XVI. The Effect of Exercise on the Time Required for the Development of the Anorexia Characteristic of Lack of Undifferentiated Vitamin B, Am. J. Physiol. **98**:589-594 (Nov.) 1931.

15. Himwich, H. E.; Goldfarb, W., and Cowgill, G. R.: Studies in the Physiology of Vitamins: XVII. The Effect of Thyroid Administration upon the Anorexia Characteristic of Lack of Undifferentiated Vitamin B, Am. J. Physiol. **99**:689-695 (Feb.) 1932.

16. Cowgill, G. R., and Dann, M.: The Failure of Dinitrophenol to Influence the Vitamin B Requirement, Yale J. Biol. & Med. **8**:501-509 (May) 1936.

17. Cowgill, G. R.; Rosenberg, H. A., and Rogoff, J.: Studies in the Physiology of Vitamins: XIV. The Effect of Administration of Large Amounts of Water on the Time Required for Development of the Anorexia Characteristic of a Deficiency of the Vitamin B Complex, Am. J. Physiol. **95**:537-541 (Dec.) 1930.

As far as the normal vitamin B_1 requirement of man is concerned, the applicability of data derived from experiments on dogs and other animals to its estimation has been abundantly proved. On the basis of of evidence that the requirement in several species is a function of the body weight and of the metabolic rate of the organism, the formula for man has been evolved (Cowgill,[18] 1934):

$$\frac{\text{Vitamins (mg.)}}{\text{Calories}} = 0.0000284 \times \text{Weight (Gm.)}.$$

In this formula the daily vitamin B_1 requirement is given in milligrams of a standard yeast concentrate (milligram equivalents), and the calories represent the individual's daily total caloric intake. The validity of this formula is established by means of extensive calculations of the vitamin B_1 content of a number of dietaries for human beings and excellent correlation between their conformity to the formula and their ability to protect against beriberi. Further confirmation of this work may be found in the study of Baker and Wright[19] (1936), and proof of the clinical usefulness of the formula has appeared in independent clinical reports (Jolliffe and Colbert,[20] 1936; Goodhart and Jolliffe,[21] 1938), showing that so-called alcoholic polyneuritis is not improved in patients whose vitamin-calory ratio is low or borderline but that marked improvement is obtained when excess vitamin B_1 is administered. As data derived from experiments on dogs have already proved useful in application to dietary problems of human beings, a study of the effect of diarrhea on the vitamin B_1 requirement of dogs may therefore be considered a valid means of approach to the question of the amount of this vitamin which should be made available to patients suffering from diseases in which chronic diarrhea is a symptom. As a result of the present study, some conclusions will be presented not only as to the quantities desirable but also as to the relative values of various sources and routes of administration of the vitamin.

In addition to the possible clinical application of determinations of the vitamin B_1 requirement of dogs with diarrhea, the data may also shed some light on the question of the mode of excretion of this factor. The fact that this vitamin is excreted in the urine and that the amount bears some relation to the dietary intake has been demonstrated by

18. Cowgill, G. R.: The Vitamin B Requirement of Man, New Haven, Conn., Yale University Press, 1934.

19. Baker, A. Z., and Wright, M. D.: Vitamin B_1 in Human Diets, Proc. Roy. Soc. Med. **29**:1145-1154 (July) 1936.

20. Jolliffe, N., and Colbert, C. N.: Etiology of Polyneuritis in the Alcohol Addict, J. A. M. A. **107**:642-647 (Aug. 29) 1936.

21. Goodhart, R., and Jolliffe, N.: Effects of Vitamin B (B_1) Therapy on the Polyneuritis of Alcohol Addicts, J. A. M. A. **110**:414-419 (Feb. 5) 1938.

Muckenfuss [22] (1918), Van der Walle [23] (1922) and Harris and Leong [24] (1936). In this connection, certain of our previous experiments (Cowgill, Rosenberg and Rogoff,[17] 1930) are interesting. They showed that diuresis produced by forcing fluids more than doubled the dog's requirement for vitamin B, as measured by the time necessary for anorexia to develop after the animal had been given an opportunity to store a maximum amount of the vitamin in the tissues and then was given a diet free from this factor. This effect was attributed to a washing out of the vitamin.

The direct estimation of the vitamin B_1 content of the feces cannot be used to determine the excretion of this material by the intestinal route, because of its presence in the stools of animals not receiving any vitamin B_1 in the diet, presumably as a result of multiplication of intestinal bacteria whose bodies contain this vitamin (Steenbock, Sell and Nelson,[25] 1923; Salmon,[26] 1925; Damon,[27] 1923 and 1924; Heller, McElroy and Garlock,[28] 1925; Sunderlin and Werkman,[29] 1928; Cowgill and Weinstein [30]).

However, indirect evidence as to the importance of the intestines in the loss of vitamin B_1 might be obtained by means of experiments in which diarrhea was produced, analogous in some respects to the diuresis experiments (Cowgill, Rosenberg and Rogoff [17]) performed in 1930. From a theoretic standpoint, diarrhea might operate to increase the body's need for vitamin B_1 by bringing about a loss of the vitamin stored in the tissues, through excretion into the intestines along with the fluid which forms so large a part of the diarrheal stool. A differentiation

22. Muckenfuss, A. M.: The Presence of Food Accessories in Urine, Bile and Saliva, J. Am. Chem. Soc. **40**:1606-1611, 1918.

23. Van der Walle, N.: The Presence of the Antineuritic and Antiscorbutic Vitamins in Urine, Biochem. J. **16**:713-726, 1922.

24. Harris, L. J., and Leong, P. C.: Vitamins in Human Nutrition: The Excretion of Vitamin B_1 in Human Urine and Its Dependence on the Dietary Intake, Lancet **1**:886-894 (April 18) 1936.

25. Steenbock, H.; Sell, M. T., and Nelson, E. M.: Vitamin B: I. A Modified Technique in the Use of the Rat for Determinations of Vitamin B, J. Biol. Chem. **55**:399-410 (March) 1923.

26. Salmon, W. D.: Vitamin B in the Excreta of Rats on a Diet Low in This Factor, J. Biol. Chem. **65**:457-462 (Sept.) 1925.

27. Damon, S. R.: Some Observations in Regard to Growth-Promoting Substances of Bacterial Origin, J. Biol. Chem. **56**:895-902 (July) 1923; Acid-Fast Bacteria as a Source of Vitamin B, J. Path. & Bact. **27**:163-169 (April) 1924.

28. Heller, V. G.; McElroy, C. H., and Garlock, B.: The Effect of the Bacterial Flora on the Biological Test for Vitamin B, J. Biol. Chem. **65**:255-264 (Aug.) 1925.

29. Sunderlin, G., and Werkman, C. H.: Synthesis of Vitamin B by Microorganisms, J. Bact. **16**:17-33 (July) 1928.

30. Cowgill, G. R., and Weinstein, L.: Unpublished data.

between the amount of the vitamin which merely escapes absorption and that which may be actively excreted through the intestinal tract can be made by arranging conditions so that in some of the experiments the dogs ingest small amounts of vitamin B_1 daily and so that impairment of absorption plays a major role, whereas in others this factor is excluded either by giving the vitamin parenterally or by inducing diarrhea only after the animals have had an opportunity to store a maximum amount of it in their tissues.

The experiments reported here are designed, therefore, with a twofold purpose, first, to obtain data which may be applicable to an estimation of the vitamin B_1 requirement of patients suffering from diarrheal conditions and, second, to contribute to available knowledge of the mode of excretion of this vitamin.

EXPERIMENTAL METHODS

The methods used in this investigation consisted of two principal procedures, both of which were derived from the observations made in 1925 (Cowgill, Deuel and Smith [13]) and were based on the production in dogs of anorexia shown (Cowgill, Rosenberg and Rogoff,[31] 1931; Burack and Cowgill,[32] 1931; Sherman and Sandels,[33] 1931) to be specific for the antineuritic vitamin B (B_1).

A group of 9 young adult mongrel dogs, weighing between 6 and 11 Kg., was employed. Every dog was observed at the beginning to have a normal appetite and was given a vermifuge to assure freedom from intestinal parasites. The diet consisted of an artificial mixture of casein, sucrose, lard, butter, bone ash and certain mineral salts, known to be practically free from vitamin B, which was described (Cowgill [34]) in 1923 and designated as the casein III diet. The supplements are listed in table 2. At the time these experiments were conducted, pure crystalline vitamin B_1 was not yet available. Since complex mixtures had to be used, widely different sources were chosen, so that if quantitatively comparable results should be obtained, they could be attributed specifically to the vitamin and not to any other components of the materials. These substances were assayed

31. Cowgill, G. R.; Rosenberg, H. A., and Rogoff, J.: Studies in the Physiology of Vitamins: XV. Some Observations of the Effect of Administration of the Antineuritic and Heat Stable Factors on the Anorexia Characteristic of Lack of the Vitamin B Complex, Am. J. Physiol. **96**:372-376 (Feb.) 1931.

32. Burack, E., and Cowgill, G. R.: Anorexia Characteristic of Lack of the Vitamin B Complex: The Roles of the Individual Components, Proc. Soc. Exper. Biol. & Med. **28**:750-752 (April) 1931.

33. Sherman, H. C., and Sandels, M. R.: Further Experimental Differentiation of Vitamins B and G, J. Nutrition **3**:395-409 (Jan.) 1931.

34. Cowgill, G. R.: Studies in Physiology of Vitamins: II. Parenteral Administration of Vitamin-B—Mammalian Experiments, Am. J. Physiol. **66**: 164-175 (Sept.) 1923.

in this laboratory, the pigeon method (Block, Cowgill and Klotz,[35] 1932) being used. The values found corresponded well with those claimed by the manufacturers.

Series 1 consisted of "saturation" experiments, in which the tissues were first given opportunity to store vitamin B_1. Each dog, after receiving a stock diet, was transferred to the casein III diet and at the same time given large portions of substances rich in vitamin B_1. Usually 50 Gm. of yeast was administered one day, followed by 50 Gm. of wheat germ the next day, or else two 50 Gm. portions of either material was given. In some instances 10 Gm. of liver extract was also administered, to make doubly sure that vitamin B_2 (or G) was also present in abundance.

The animal was then allowed to subsist on the vitamin B_1 deficient diet, a daily weighed amount being provided which was sufficient for its caloric needs. Invariably a day came, after a period varying for different animals from ten to twenty-four days, when only a part of the ration was consumed, and on the following day part of or all the food was again refused. The number of days during which there was a perfect appetite was taken as the significant figure, but the experiment was not considered complete until checked as follows: The dog was given

TABLE 2.—*Sources of Vitamin B_1*

	Vitamin B_1 Value	
	Milligram Equivalents*	U. S. P. Units
Yeast, dried brewers' †	116 per Gm.	5.8 per Gm.
Wheat germ ‡	132 per Gm.	6.6 per Gm.
Rice polishings extract §	1,193 per cc.	59.6 per cc.

* One milligram equivalent (Cowgill,[18] 1934) equals 0.05 U. S. P. units.
† Supplied by the Northwestern Yeast Co., Chicago.
‡ The wheat germ used was embo, a product of General Mills, Inc., Minneapolis, supplied for experimental purposes by Dr. C. H. Bailey, director of research.
§ An extract suitable for subcutaneous injection was made by Eli Lilly Co. according to the method previously described (Stuart, Block and Cowgill,[27] 1934). The concentrate was furnished for this research project by D. H. W. Rhodehamel, director of research.

a small dose of beef extract [36] which was free from vitamin B_1 and one or two days later a small dose of a potent source of the vitamin. In every case the appetite for the usual daily amount of the casein III diet was restored by the latter for at least one day but never by the former.

The dog was then brought as nearly as possible to the same nutritional condition as before the experiment was begun by being given the stock diet, usually for at least three weeks before the next experiment was started. In this experiment the effect of diarrhea was determined. A procedure identical with that previously described was used, except that beginning on the day after the second large dose of vitamin B_1 was given, magnesium sulfate was administered daily. This saline cathartic was chosen in order to produce mild diarrhea, compatible with maintenance of normal weight and health. This drug acts on both the small and the large intestine by osmosis, causing retention and excretion of water in the alimentary tract, with little of the irritative and toxic actions characterizing

35. Block, R. J.; Cowgill, G. R., and Klotz, B. H.: The Antineuritic Vitamin: I. The Method of Assay, Concentration of the Vitamin with Silver Under Various Conditions, and Its Solubility in Certain Organic Solvents, J. Biol. Chem. **94**: 765-782 (Jan.) 1932.

36. Liebig's extract of beef, lemco, was used.

other types of purgatives. Dogs receiving enough magnesium sulfate daily to cause loose or fluid stools for weeks at a time appeared as healthy and lively as when they were not receiving the drug and did not lose weight. Usually from 3 to 5 Gm. was found sufficient. The drug was given in gelatin capsules at the same time that the food was put into the cage. Considerable individual variation was seen in the time of day at which the soft or fluid stools appeared, the average time being about eight hours after the administration of the laxative.

In series 2 and 3, which differed only as to the form in which the vitamin was administered, the guiding principle of the experiment was that of preventing anorexia by the smallest possible daily dose of vitamin B_1 while the animal was receiving the deficient diet.

In the experiments in series 2 each dog was allowed to subsist on the ration that was free from vitamin B_1 until anorexia developed. The next day a supplement containing vitamin B_1 was given, usually 0.3 Gm. of yeast or wheat germ per kilogram. If the animal refused to eat all its daily portion of the casein III diet, the dose of the vitamin preparation was increased, usually by about 0.2 Gm. Similar increments were added each day until a dose was reached which caused the appetite to be restored. This apparently adequate dose was continued for ten days.

In other dogs the trial dose was found sufficient to maintain the appetite. In these cases the initial dose was continued daily for ten days, after which it was decreased, usually by about 10 per cent. This procedure was repeated until a dose was reached at which the dog refused to eat all its ration for two or more days. The previous dose, with which it had eaten well for ten days, was then administered, and usually the appetite was restored. A difference of 0.2 Gm. per day in the total dose of the yeast or wheat germ given by mouth usually made the difference between refusal of at least part of the diet free from vitamin B_1 and willingness to eat the entire portion. In some cases when the animals did not immediately consume all the vitamin supplement from a dish, the vitamin was given in gelatin capsules.

The requirement for each dog was determined by the method outlined in two periods, one in which there was no diarrhea and the other in which the dog received sufficient magnesium sulfate to produce liquid stools daily. In some instances the period of diarrhea preceded the one without diarrhea, and in some it followed this period. In some cases the required dosage was reached by increasing doses and in some by decreasing ones.

This method possesses the advantages that the daily requirement can be stated in units of vitamin B_1 and that a comparison can be made between different substances and also between various routes of administration. The justification for using a period as short as ten days in establishing the criterion of the minimal daily dose is that in a number of preliminary experiments not included in this paper it was found that the results for any dog could be obtained again with fairly reasonable agreement (table 5, dog 2). Also, the average daily requirement of orally administered vitamin B_1 found under normal conditions by this method (35.5 milligram equivalents per kilogram of body weight) corresponds closely with the value (40 milligram equivalents per kilogram per day) obtained (Cowgill, Deuel and Smith,[18] 1925) for dogs which were maintained on the minimal daily dose necessary to preserve appetite for two months or more.

The procedure in series 3 was identical with that in series 2, except that instead of an oral dose of vitamin B, a source of this vitamin was administered subcutaneously in the form of a rice polishings concentrate. The preparation as

obtained from the manufacturer (Stuart, Block and Cowgill,[37] 1934) was diluted ten times with sterile physiologic solution of sodium chloride and administered with aseptic precautions. As a trial dose for starting, 0.02 cc. per kilogram was the usual amount, and after the end point had been reached, a difference of 0.02 cc. in the total dose was usually significant.

It is apparent that either parenteral administration or the method used in series 1, in which the animals were given sufficient vitamin B_1 before diarrhea started to saturate their tissues, would obviate the loss of vitamin by failure of intestinal absorption. On the other hand, in series 2, in which the vitamin was given in daily oral doses, it might be expected that lack of absorption during diarrhea would play a major role. By these varied procedures any excretion of vitamin B_1 through the intestinal tract, which might be enhanced by the diarrhea, could be distinguished from simple failure of absorption.

TABLE 3.—*Effect of Diarrhea on Vitamin B_1 Requirement of Dogs After "Saturation" Doses (Series 1)*

Dog	Without Diarrhea		With Diarrhea		
	Body Weight, Kg.	Period of Perfect Food Intake (*a*), Days	Body Weight, Kg.	Period of Perfect Food Intake (*b*), Days	Difference Between *a* and *b*, Days
1	11.2	12	11.1	15	+3
2	9.2	13	8.9	12	−1
3 (*a*)	8.0	14			
(*b*)	7.3	10			
		Average 12	10.3	12	0
4	7.5	11	8.7	12	+1
5	9.9	24	10.7	18	−6
6	6.2	22	7.5	17	−5

RESULTS

The results of series 1 (table 3) indicate that diarrhea following adequate storage of vitamin B_1 has little effect on the time required for depletion to the level of anorexia. For 4 of the 6 dogs studied by this method the differences in length of the period of perfect appetite with and without diarrhea were no, one, one and three days, respectively, which are within the limit of error of the method, as illustrated by the difference of four days found in 2 experiments without diarrhea on the same dog (dog 3, table 3). In 2 others the periods of diarrhea were shorter by five or six days than the control period. These can hardly be considered of much significance when compared with previous experiments (Cowgill, Rosenberg and Rogoff,[17] 1930) which showed that diuresis decreased the time necessary for depletion in 4 dogs from nineteen, twenty-two, thirty-three and twenty days to eight, ten, fifteen and

37. Stuart, E. H.; Block, R. J., and Cowgill, G. R.: The Antineuritic Vitamin: V. The Preparation of a Vitamin Concentrate Suitable for Parenteral Use, J. Biol. Chem. **105**:463-466 (June) 1934.

eleven days, respectively. It seems evident, therefore, that when the animals are not receiving vitamin B_1 by mouth and the question of failure of absorption due to diarrhea is not involved, the rate of loss of stored vitamin B_1 from the body is not accelerated by diarrhea.

In marked contrast were the results when tissue stores were lowered and daily oral doses of vitamin B_1 were administered (table 4). When mild diarrhea was induced under these conditions, without exception there was a definite increase in the amount of the vitamin required. This increase ranged from 18 to 82 per cent. It is obvious that the increase can be accounted for simply by the failure of absorption of the food materials containing vitamin B_1. It is noteworthy that the concomitant loss of part of the caloric value of the ingested food did not prevent the failure of appetite which is characteristic of vitamin B_1 deficiency.

The consistent increase in requirement seen with the daily oral doses (table 4) was absent in series 3 (table 5), in which the daily dose of vitamin B_1 was given parenterally. With the exception of dog 2, which showed a marked increase, the amounts of rice polishings concentrate needed to maintain appetite when the dogs were subjected to diarrhea were not significantly larger than those needed in the absence of diarrhea, being 0, 0, 1.2, 3.6 and 4.8 milligram equivalents per kilogram. Differences of less than 6 milligram equivalents per kilogram may be regarded as insignificant, as such a difference was found between 2 experiments on the same dog (dog 2, table 5) without diarrhea. It is apparent that the results for 5 of 6 dogs confirm those in series 1. No explanation can be offered for the anomalous behavior of dog 2.

It may be observed that the average value for the requirement of the vitamin given parenterally was 25 milligram equivalents per kilogram per day without diarrhea and, excluding dog 2, 25.5 milligram equivalents with diarrhea. The apparently lower requirement of vitamin B_1 by this route as compared to that administered orally is of little significance in view of the wide range of individual variation.

So far as the bearing of these results on the question of the excretion of vitamin B_1 is concerned, they indicate that no significant amounts of vitamin B_1 are lost by excretion into the intestinal tract when its activity is stimulated and fluid loss is encouraged by diarrhea induced with magnesium sulfate. The possibility of excretion in the bile (Muckenfuss,[22] 1918) is by no means excluded. However, if these results are considered in conjunction with those obtained in 1930 (Cowgill, Rosenberg and Rogoff [17]), it appears probable that the chief route of excretion of vitamin B_1 is by way of the kidney.

CLINICAL APPLICATIONS

According to the previously mentioned formula (Cowgill,[18] 1934) a normal person weighing 66 Kg. should ingest a diet having a vitamin-

TABLE 4.—*Effect of Diarrhea on Requirement of Vitamin B_1 Administered in Daily Oral Doses (Series 2)*

		Daily Dose											
		Without Diarrhea				With Diarrhea				Increase			
Dog	Source of Vitamin B_1*	Body Weight, Kg.	Gm.	Gm. per Kg.	Milligram Equivalents per Kg.	Body Weight, Kg.	Gm.	Gm. per Kg.	Milligram Equivalents per Kg.	Gm.	Gm. per Kg.	Milligram Equivalents per Kg.	Percentage
1	Yeast†	10.7	2.2	0.20	23.2	11.1	3.0	0.27	31.3	0.8	0.07	8.1	17.5
						More than				More than			
2	Yeast†	8.7	1.7	0.20	23.2	10.0	3.1	0.31	36.0	1.4	0.11	12.8	82.0
3	Embo‡	7.9	2.0	0.25	33.0	9.3	3.0	0.32	42.2	1.0	0.07	9.2	50.0
4	Yeast†	7.3	1.7	0.23	26.7	7.8	2.0	0.26	30.2	0.3	0.03	3.5	18.0
7	Embo‡	6.0	2.8	0.47	62.0	6.3	3.5	0.56	73.9	0.7	0.09	11.9	25.0
						More than				More than			
8	Embo‡	5.2	1.8	0.35	46.2	5.2	3.0	0.58	76.6	1.2	0.23	30.4	67.0

* For a description of these sources of vitamin B_1 see table 2.
† One gram equals 116 milligram equivalents.
‡ One gram equals 132 milligram equivalents.

TABLE 5.—*Effect of Diarrhea on Daily Parenteral Dose of Vitamin B_1 Required to Maintain Appetite in Dogs (Series 3)*

	Daily Dose*										
	Without Diarrhea				With Diarrhea				Increase		
Dog	Body Weight, Kg.	Cc.	Cc. per Kg.	Milligram Equivalents per Kg.	Body Weight, Kg.	Cc.	Cc. per Kg.	Milligram Equivalents per Kg.	Cc.	Cc. per Kg.	Milligram Equivalents per Kg.
1.....	11.1	0.18	0.016	19.1	11.7	0.24	0.020	23.9	0.06	0.004	4.8
2 (*a*).....	9.7	0.28	0.029	34.6	10.0	0.44	0.044	52.5	0.16	0.015	17.9
(*b*).....	10.0	0.24	0.024	28.6	11.1	0.50	0.055	65.6	0.26	0.031	37.0
Average				31.6				59.0			27.4
3.....	9.1	0.16	0.018	21.5	9.3	0.18	0.019	22.7	0.02	0.001	1.2
4.....	7.6	0.20	0.026	31.0	8.4	0.22	0.026	31.0	0.02	0.000	0
5.....	9.0	0.24	0.027	32.2	8.9	0.24	0.027	32.2	0.00	0.000	0
9.....	8.6	0.10	0.012	14.3	8.1	0.12	0.015	17.9	0.02	0.003	3.6

* Rice polishings concentrate, 1 cc. of which is equivalent to 1,193 milligram equivalents.

calory ratio of at least 1.87. The minimum ratio for an adult weighing 35 Kg. is 1 and for one of 80 Kg., 2.25. Values between 1.8 and 2 are "too close to the minimum to be satisfactory." The "average American diet" described by Sherman[38] (1924) has been calculated (Cowgill,[39]

38. Sherman, H. C.: Chemistry of Food and Nutrition, New York, The Macmillan Company, 1924, p. 391.

39. Cowgill,[18] p. 186.

1934) to contain 6,847 milligram equivalents of vitamin B_1 and 2,500 calories, giving a vitamin-calory ratio of 2.74, well above the borderline for all but unusually large persons and nearly 50 per cent above the average minimum requirement.

The amount of vitamin B_1 contained in such a diet may be appreciated more readily if one considers that 6,847 milligram equivalents is equivalent to 6 cc. of the rice polishings concentrate used in the animal experiments of this study or to something under 2 ounces of brewers' yeast or of wheat germ (59 and 52 Gm., respectively).

The experiments of series 2 (table 3) show that in dogs with mild diarrhea there is a rise of from 20 to 80 per cent in the daily oral requirement of vitamin B_1. This suggests that if a human being receiving an ordinary adequate diet should suffer from an analogous degree of diarrhea, his margin of safety, which would average 50 per cent, might easily be wiped out, and that if he continued to subsist on his original diet for any length of time he might be in danger of at least a mild degree of vitamin B_1 deficiency. This possibility would be increased by a change to a low residue diet which, because of the omission of many of the best sources of vitamin B_1, such as whole wheat, oatmeal, bran, nuts and many vegetables, is likely to have a vitamin-calory ratio of not more than 2.2 to 2.5. A more pronounced degree of diarrhea would still further increase the danger, and it is not difficult to see how in extreme cases the pronounced deficiency states described by Mackie [4] (1935) and others might develop.

A calculation of the vitamin B value of the supplement recommended by Bahgen and Victor [8] (1931), 200 mg. of brewers' yeast three times a day, reveals that this amounts to only 69.6 milligram equivalents, which would be insignificant in supplying the needs of the individual, contributing an amount of vitamin B_1 equivalent to only 1 per cent of the "average American" daily dietary intake.

In the light of the present study some suggestions may be made in regard to the treatment of patients with chronic diarrhea. It is unwise to place much reliance on the fact that before the diarrhea developed the patient may have been in an excellent state of nutrition, for vitamin B_1 is not stored in the body in quantities sufficient to protect against the effects of prolonged deficiency. The appearance of anorexia in such cases should be regarded as a warning sign that the supply of this dietary essential which is being absorbed may be inadequate. Even for a patient whose appetite continues to be good, the diet should be planned to assure a continued intake of enough vitamin B_1.

The vitamin B_1 value of the basic diet tolerated by the patient, whether the ordinary diet to which he was accustomed before the disease became manifest or a special diet, such as one low in roughage, can

be calculated by the physician or the dietitian from tables that have been published in volumes on vitamins, by Cowgill [40] and in many handbooks of dietetics. By adding up the caloric content of the foods comprising the diet and dividing the total number of milligram equivalents of vitamin B_1 by the total number of calories, the vitamin-calory ratio can be obtained. This, of course, is of greatest value when calculated on the basis of an accurate record of the food actually ingested by the patient.

The minimum vitamin-calory ratio required by an individual, if he is an adult, depends on his body weight. The value can be calculated by the formula given previously or can be more simply found by applying the chart that has been formulated (Cowgill,[41] 1934). This chart may be approximately reproduced by plotting on simple graph paper the values of the vitamin-calory ratio for body weights of 30 and 80 Kg. (0.85 and 2.25, respectively) and connecting them with a straight line.

It is advised that after the minimum vitamin-calory ratio required by the patient has been ascertained and the ratio provided by the diet he is receiving has been calculated, his vitamin B_1 intake should be increased by means of some supplement, so that if the diarrhea is mild he receives a vitamin-calory ratio of at least double the calculated minimum; if the diarrhea is moderately severe the vitamin-calory ratio should be three times the minimum.

The form in which the vitamin should be provided depends on the symptoms. If the patient manifests signs of vitamin B_1 deficiency or of multiple deficiencies, it is obvious that the vitamin should be administered, along with other vitamins or any other dietary essentials indicated, in high dosage, in concentrated form and perhaps parenterally. For this purpose there are available concentrates of liver, of yeast and of rice polishings, some of which are suitable for intramuscular injection, and it is now possible to obtain the pure crystalline vitamin. In such cases the relatively high cost of these preparations is of small moment compared with the urgency of immediate administration of the vitamin in amounts large enough to have the desired therapeutic effect. Some patients in whom there is no manifest avitaminosis or in whom the only suggestion of this is some degree of anorexia may nevertheless be vomiting, or the diarrhea may be sufficiently severe so that parenteral administration may be indicated.

For the majority of patients showing diarrhea, however, it is preferable to give the extra vitamin in the form of foods rich in vitamin B_1, the most notable examples being brewers' yeast and wheat germ. Many excellent preparations of both of these materials are now on the market. In a few cases, a combination of the more rapidly acting concentrated

40. Cowgill,[18] pp. 87-93.
41. Cowgill,[18] p. 110.

sources and the more economical food supplements may prove most helpful. The physician should in every case prescribe products the biologic potency of which has been quantitatively determined by properly controlled animal tests.

SUMMARY AND CONCLUSIONS

The vitamin B_1 requirement of dogs with and without mild but persistent diarrhea was determined in three series of experiments. In series 1 the relative requirements were determined by observing the length of time necessary for anorexia to develop when the animals received a diet deficient in vitamin B_1 after large doses of the vitamin which permitted storage in the tissues. No significant increase in the requirement during the period of diarrhea was found by this method.

In series 2 the actual minimum oral dose needed to maintain appetite was determined. This averaged 35.5 milligram equivalents (Cowgill) per kilogram per day in the period in which there was no diarrhea. A marked increase in the daily requirement, of from 18 to 82 per cent, occurred as a result of diarrhea. The procedure in series 3 was similar to that in series 2 except that the doses were administered subcutaneously. Five of 6 dogs showed no significant increase in the requirement as a result of diarrhea. The average daily requirement of parenterally administered vitamin B_1 was 25 milligram equivalents per kilogram.

These results are interpreted to mean that failure of absorption, which would be prominent in series 2 but excluded in series 1 and 3, is the only important mechanism by which diarrhea increases the vitamin B_1 requirement. In conjunction with the previous study (Cowgill, Rosenberg and Rogoff,[17] 1930), in which an enormous increase in the vitamin B_1 requirement was produced in dogs by diuresis, these experiments appear to indicate that the urinary system and not the gastrointestinal tract is the principal route of excretion of vitamin B_1.

Clinical observations by a number of authors are cited, revealing that avitaminosis, especially of the B complex, is a not infrequent complication of chronic diseases of the gastrointestinal tract in which diarrhea is a symptom. Chronic ulcerative colitis is a conspicuous example of such conditions. A plan is offered whereby the dietary management of diseases of this class with respect to the intake of vitamin B_1 can be placed on a more nearly quantitative basis than has been possible in the past.

CHANGE IN PLASMA VOLUME DURING RECOVERY FROM CONGESTIVE HEART FAILURE

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In a lecture delivered before the Royal College of Surgeons in February 1896, Starling [1] predicted on theoretic grounds that "hydraemic plethora" must accompany congestive heart failure. Thirteen years later he was able to confirm the prediction by direct observation of a dog suffering from chronic myocardial insufficiency.[2] By bleeding the ailing animal he recovered 500 cc. of blood, as compared with 300 cc. from a normal dog of the same size. In 1902 Smith,[3] using the Haldane carbon monoxide inhalation method of determining the volume of the blood, demonstrated a state of plethora in a case of congestive heart failure due to an adherent pericardium. Although Bock [4] reported finding a normal blood volume in a case of cardiac failure, more recent investigations with carbon monoxide inhalation and various dye methods [5] have

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1. Starling, E. H.: Physiological Factors Involved in the Causation of Dropsy, Lancet **1**:1407, 1896.

2. Bolton, C., and Starling, E. H.: Note on the Blood Pressure and Lymph Flow in a Case of Heart Disease in a Dog, Heart **1**:292, 1909-1910.

3. Smith, L. J., and McKisack, H. L.: On a Case in Which Cyanosis and Plethora Occurred in Association with Adherent Pericardium, Tr. Path. Soc. London **53**:136, 1902.

4. Bock, A. V.: The Constancy of the Volume of the Blood Plasma, Arch. Int. Med. **27**:83 (Jan.) 1921.

5. (*a*) Keith, N. M.; Rowntree, L. G., and Geraghty, J. J.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915. (*b*) Brown, G. E., and Rowntree, L. G.: The Volume and Composition of the Blood and the Changes Incident to Diuresis in Cases of Edema, ibid. **35**:129 (Jan.) 1925. (*c*) Plesch, J.: Kreislaufsprobleme, Deutsche med. Wchnschr. **52**:1159, 1926. (*d*) Hitzenberger, K., and Tuchfeld, F.: Die zirkulierende Blutmenge bei Kreislauferkrankungen im kompensierten und dekompensierten Zustand, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **41**:358, 1929. (*e*) Wollheim, E.: Kompensation und Dekompensation des Kreislaufs, Klin. Wchnschr. **7**:1261, 1928; Zirkulierende Blutmenge, Kompensation und Dekompensation des Kreislaufes, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **41**:352, 1929. (*f*) Schürmeyer, A.: Ueber Blutmengenbestimmungen bei Herzfehlern, ibid. **40**:388, 1928. (*g*) Landau, A.; Markson, M.; Goliborska, T., and Lewicki, I.: Sur la quantité du sang circulant et sur son comportement dans l'insuffisance cardiaque chronique, Arch. d. mal. du cœur **27**:453, 1934.

indicated abnormally high blood volumes for patients suffering from uncomplicated heart failure.[6] In addition, these studies have shown a decrease in blood volume during recovery from myocardial failure.[7] In spite of the agreement of the numerous independent reports, the reliability of the methods employed by these investigators has been seriously questioned.[8]

Various investigators [9] have attempted to illuminate the problem of the blood volume in heart failure by studying the red blood cell count

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6. In a small group of cases of congestive heart failure complicated by chronic pulmonary disease, Wollheim,[5e] and Hitzenberger and Tuchfeld[5d] found low blood volumes.

7. Wollheim.[5e] Schürmeyer.[5f] Laudau and others.[5g] Levin, E.: La accion immediata de la digital sobre el volumen de la sangre circulante, Rev. Soc. argent. de biol. **11**:75, 1935. Mies, H.: Ueber die Wirkung des Strophanthin auf die zirkulierende Blutmenge, Ztschr. f. Kreislaufforsch. **23**:460, 1931.

8. (*a*) Griesbach, W.: Eine klinische brauchbare Methode der Blutmengenbestimmung, Deutsche med. Wchnschr. **47**:1289, 1921. (*b*) Seyderhelm, R., and Lampe, W.: Die Blutmengenbestimmung und ihre klinische Bedeutung, Ergebn. d. inn. Med. u. Kinderh. **27**:245, 1925. (*c*) Heilmeyer, L.: Das Verhalten des Kongorots zu den Serumkolloiden, zugleich ein methodischer Beitrag zur Blutmengenbestimmung mit Kongorot nach Griesbach, Biochem. Ztschr. **212**: 430, 1929. (*d*) Smith, H. P.: Determination of Plasma Volume, J. Exper. Med. **51**:369, 1930; Blood Volume Studies, Am. J. Physiol. **51**:221, 1920. (*e*) Graff, S., and Clarke, H. T.: Determination of Plasma Volume, Arch. Int. Med. **48**: 808 (Nov.) 1931. (*f*) Uhlenbruck, P., and Leyendecker, T.: Stufenphotometrische Blutplasmamengenbestimmungen bei Herzkranken, Normalpersonen und nach sportlichen Anstrengungen, Ztschr. f. klin. Med. **118**:164, 1931. (*g*) Brockmann, H.: Ein Beitrag zur Frage der Bestimmung der zirkulierenden Blutmenge beim normalen lebenden Menschen mit der Farbstoff-Injektionsmethode, unter Benutzung des Pulfrischen Stufenphotometers, Ztschr. f. d. ges. exper. Med. **87**:208, 1933. (*h*) Sunderman, F. W.: The Measurement of Serum Volume, J. Biol. Chem. **109**:xci, 1935. (*i*) Gregersen, M. I.; Gibson, J. J., and Stead, E. A.: Plasma Volume Determination with Dyes: Errors in Colorimetry; Use of the Blue Dye T-1824, Am. J. Physiol. **113**:54, 1935.

9. (*a*) Reiss, E.: Die refraktometrische Blutuntersuchung und ihre Ergebnisse für die Physiologie und Pathologie des Menschen, Ergebn. d. inn. Med. u. Kinderh. **10**:613, 1913. (*b*) Albrecht, C.: Untersuchungen über den Wasserwechsel im Blut bei kardialen Stauungen, Deutsches Arch. f. klin. Med. **171**:595, 1931. (*c*) Veil, W. H.: Ueber die klinische Bedeutung der Blutkonzentrationsbestimmung, ibid. **112**:504, 1913; **113**:226, 1914; Physiologie und Pathologie des Wasserhaushaltes, Ergebn. f. inn. Med. u. Kinderh. **23**:648, 1923. (*d*) Nonnenbruch, W., in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol. 17, p. 285. (*e*) Beckman, K.: Oedemstudien, Deutsches Arch. f. klin. Med. **135**:39, 1921. (*f*) Askanasy, S.: Ueber den Wassergehalt des Blutes und Blutserums bei Kreislaufstörungen, Nephritiden, Anämien und Fieber nebst Vorbemärkungen über die Untersuchungenmethoden und über den Befund unter physiologischen Verhältnissen, ibid. **59**:385, 1897. (*g*) Grawitz, E.: Ueber die Veränderungen der Blutmischung infolge von Circulationsstörungen, ibid. **54**:588, 1895.

and the concentration of protein in the plasma. The red blood cells were studied by the usual counting technic and the plasma protein by the refractive index method. Since there is considerable experimental error in each of these methods, it is not surprising that the results obtained were somewhat contradictory. Reiss,[9a] for instance, found the plasma protein concentration low in congestive heart failure, while Veil [9c] found it usually normal or slightly increased. Albrecht [9b] and Reiss noticed an appreciable increase in the red blood cell count and the plasma protein concentration in certain cases during recovery from heart failure, whereas Veil,[9c] Nonnenbruch [9d] and Beckman [9e] found little if any change.

The purpose of this paper is to report a study by more refined methods of the red blood cell count and the plasma protein concentration during recovery from congestive heart failure and to point out the relation of the observed changes to the volume of plasma.

METHODS

Changes in the number of circulating red blood cells were determined by measuring the volume of packed red blood cells. The limit of error in hematocrit measurements is definitely smaller than in the ordinary red blood cell count.[10] Hemoglobin determinations and red blood cell counts were done, in addition, on many of the samples of blood. The determinations were made on oxalated blood drawn from the antecubital vein, the proper concentrations of potassium and ammonium oxalate being added to prevent any change in the size of the red blood cells.[11] The plasma protein concentration was measured by the macro-Kjeldahl method,[12] which is considerably more accurate than refractometer methods. The albumin-globulin ratio was determined in 4 of the 10 cases, since its value should remain constant if the changes in plasma protein concentration are due merely to loss of water from the plasma.

RESULTS

The data obtained from study of the red blood cell count, hemoglobin concentration, volume of packed red blood cells and plasma protein concentration for 10 patients recovering from congestive heart failure are tabulated in the accompanying table. Patients suffering from rheumatic, syphilitic, hypertensive and arteriosclerotic heart disease were included in the series. The initial determinations were made on the day of the patient's admission to the hospital before treatment

10. Wintrobe, M. M.: Blood of Normal Young Women Residing in a Subtropical Climate, Arch. Int. Med. **45**:287 (Feb.) 1930.

11. Wintrobe, M. M.: A Standardized Technique for the Blood Sedimentation Test, Am. J. M. Sc. **189**:102, 1935.

12. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: II. Methods, Baltimore, Williams & Wilkins Company, 1932, p. 698.

13. Footnote deleted on proof.

Changes in the Blood During Recovery from Congestive Heart Failure

Patient No.	Initials	Age	Race	Sex	Clinical Data	Day	Reading, % Hematocrit	Erythrocytes, Million	Hemoglobin, %	Protein, Gm. per 100 Cc.	Albumin-Globulin Ratio
1	M. N.	52	N	F	Arteriosclerosis; auricular fibrillation; rales; enlarged liver; moderate edema	1	44	5.0	100	5.2	66/34
						5	52	6.0	110	6.2	58/42
						17	51	...	...	...	.....
2	J. E.	61	W	M	Rheumatic endocarditis; auricular fibrillation; cyanosis; rales; enlarged liver; marked edema	1	46	4.5	90	5.4	.....
						2	47	...	...	...	.....
						6	53	6.4	120	6.2	.....
						10	56	...	...	...	.....
						17	56	...	...	5.7	.....
3	D. B.	39	N	M	Syphilis (?); syphilitic myocarditis; rales; enlarged liver; moderate edema	1	42	4.0	88	5.6	.....
						6	48	5.5	110	6.0	.....
4	W. S.	56	W	M	Arteriosclerosis; thyrotoxicosis; auricular fibrillation; rales; enlarged liver; moderate edema	1	40	4.5	90	6.1	.....
						4	50	6.0	100	6.9	.....
						24	..	5.4	94	...	.....
5	W. H.	56	N	M	Syphilitic aortitis; anasarca; enlarged liver; venous pressure, 245 mm.	1	40	4.0	82	6.5	47/53
						5	..	5.0	110	9.1	41/59
						10	55	...	...	...	.....
						24	51	4.7	90	8.4	41/59
6	S. G.	44	N	M	Hypertension; arteriosclerosis; rales; moderate edema; enlarged liver; venous pressure, 195 mm.	1	48	5.3	108	6.3	46/54
						2	46	...	...	...	.....
						3	59	7.6	135	7.8	49/51
						4	61	...	...	...	.....
						5	61	7.8	135	...	.....
						6	62	...	...	...	.....
						9	58	...	...	...	.....
7	C. B.	76	W	M	Arteriosclerosis; auricular fibrillation; few rales; slightly enlarged liver; moderate edema	1	37	3.7	82	5.9	.....
						4	41	3.9	88	6.1	.....
8	J. S.	48	N	M	Syphilitic aortitis; rales; slightly enlarged liver; moderate edema	1	..	3.3	77	5.4	.....
						4	..	4.5	90	6.0	.....
9	N. B.	54	W	M	Hypertension; rales; enlarged liver; moderate edema	1	38	4.2	79	5.1	.....
						2	39	4.3	83	...	.....
						3	41	...	...	...	.....
						4	43	...	...	...	.....
						5	43	4 8	94	5.2*	.....
10	H. H.	73	N	F	Hypertension; auricular fibrillation; rales; moderate edema; enlarged liver; persistent bradycardia †	1	44	5.0	100	5.2	66/34
						5	52	6.0	110	6.0	58/42
						17	51	...	...	...	.....

* Marked albuminuria was noted throughout the patient's stay in the hospital.

† No digitalis was given because of persistent bradycardia. Urea, caffeine citrate and ammonium chloride were administered to promote diuresis.

was started. None of the patients had been taking digitalis at the time of entry, and all showed signs of failure of both the right and the left side of the heart, with moderate to marked peripheral edema. Each patient was digitalized immediately except patient 10, who because of persistent bradycardia was not given digitalis. None of the patients received diuretics (other than digitalis) except patient 10 (table).

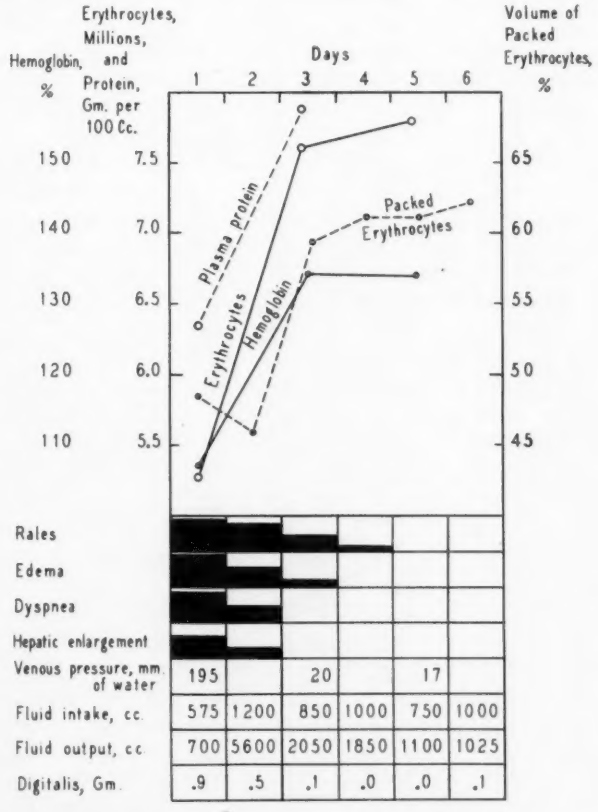

Chart 1 (patient 6).—Hemoconcentration during recovery from congestive heart failure.

An analysis of the data reveals a definite rise in the concentration of hemoglobin, red blood cell count and plasma protein value during the first few days of treatment. The change in composition of the blood was observed to occur at the time of the diuresis and disappearance of edema. The data for patient 6 are plotted in chart 1

and illustrate the magnitude of the change and the rapidity with which it may take place in certain cases. Chart 2 shows the striking rise in the concentration of hemoglobin and in the red blood cell count which may occur even in spite of venesection. The data for patient 10 indicate that the same changes in the blood may occur without digitalis therapy, the diuresis in this case having been brought about by rest in bed and mild diuretics.

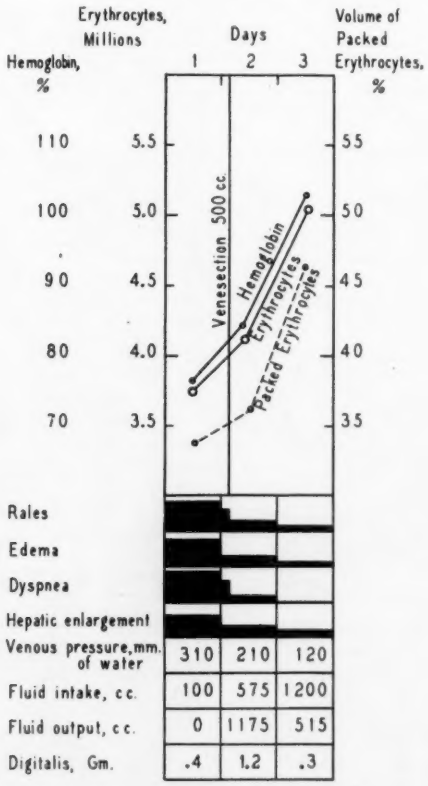

Chart 2.—Chart showing the increase in the red blood cell count during recovery from congestive heart failure in spite of venesection. The venous pressure on the second day was taken before venesection. The fluid output for the second day includes the amount removed by venesection.

COMMENT

Such marked rises in hemoglobin value, red blood cell count and volume of packed red blood cells occurring within three to six days can be explained in only two ways—either the absolute number of red

blood cells in the circulation must increase, possibly because more red blood cells are washed into the actively circulating blood stream from previously congested areas, or else the volume of the plasma must decrease, causing a concentration of the cells. That the first explanation is inadequate is obvious from the fact that there occurs a rise in the concentration of plasma protein that is roughly proportional in the majority of cases to the increase in red blood cells. An increase in the protein value cannot, of course, be accounted for by any such mechanism as that suggested in the first explanation since the protein is in solution in the plasma. The rapid proportionate increase in the red blood cell count and the plasma protein value (with the maintenance of a relatively constant albumin-globulin ratio in every case in which this factor was studied) seems to point definitely to a loss of fluid from the blood plasma.

That the plasma volume should be increased in congestive heart failure and should return to normal during recovery seems logical in view of certain well established facts relating to the pathologic physiology of cardiac insufficiency. Chronic passive congestion of the lungs, which is observed in nearly all cases of heart failure, is associated with an increase in the volume of blood in the pulmonary vascular bed, as evidenced by a decrease in the patient's vital capacity.[14] The volume of blood in the heart and lungs has been shown by Hamilton, Moore, Kinsman and Spurling [15] to be greatly increased in congestive failure, sometimes by as much as 2,000 cc. If the right ventricle as well as the left has failed, the volume of blood in the systemic venous bed likewise is increased, as evidenced in the living patient by engorgement of superficial veins, increased venous pressure and noticeable enlargement of the liver and sometimes of the spleen. The large volume of blood transferred to the pulmonary vessels and to the systemic veins is lost to the arterial circulation, and were the arterial circulation not able to compensate for the loss of blood, the patient would soon pass into a state of shock. As in the case of hemorrhage, however, the arterial blood pressure is undoubtedly maintained temporarily by a decrease in the volume of the arterial vascular bed, brought about by local vasoconstriction, and more permanently by an increase in the total volume of blood resulting from retention of water in the plasma. Just as the blood of a patient suffering a large hemorrhage must become diluted, so must the plasma volume of a patient suffering from congestive heart failure be increased.

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14. Harrison, T. R.: Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1935.

15. Hamilton, W. F.; Moore, J. N.; Kinsman, J. M., and Spurling, R. G.: Studies on the Circulation, Am. J. Physiol. **99**:534, 1932.

If the water content of the plasma is increased in heart failure, there should be a decrease both in the red blood cell count and in the plasma protein concentration. Payne and Peters,[16] and Herrmann,[17] using the most accurate methods of measurement, have reported low plasma protein concentrations in a large series of cases of heart failure. The data given in the accompanying table also show a definite tendency toward low plasma protein values. The red blood cell data, however, as well as the data reported by Albrecht,[9b] Askanasy,[9f] Grawitz [9g] and others, fail to show abnormally low red blood cell counts in most of the cases of congestive failure studied. This apparent discrepancy may be explained by an increase in the hemopoietic activity of the bone marrow, which raises the absolute number of red blood cells in the circulation and thereby compensates for the dilution. Evidence that the bone marrow may be stimulated is supplied by the fact that, first, polycythemia is not uncommonly observed in heart failure and, secondly, patients showing normal red blood cell counts during heart failure show marked polycythemia during recovery (patients 1 to 4, 6 and 10).

The magnitude of the changes in plasma volume indicated by the present study should be emphasized. Assuming that patient 6 (chart 1) when there was good compensation had a plasma volume of about 2.5 liters, the observed changes in the blood indicate that the plasma volume was approximately 4 liters when he was admitted to the hospital and fell roughly 1.5 liters in forty-eight hours. More important still, the rise of 1.5 Gm. in the plasma protein value during the same period causes, according to Govaerts' [18] data, an increase of 80 mm. of water in the oncotic pressure of the plasma. As one of the most important factors in controlling the passage of water between the blood and the tissue spaces is the plasma oncotic pressure, the significance of this rise at once becomes apparent. A rise in the oncotic pressure of this order of magnitude undoubtedly plays an important part in the withdrawal of edema fluid from the tissues during recovery from heart failure and is a factor which has been almost entirely overlooked in the study of cardiac edema.

In conclusion, it should be emphasized that the method used in the present study for detecting changes in plasma volume has definite limitations. First, only the grossest change can be demonstrated by the red

16. Payne, S. A., and Peters, J. P.: The Plasma Proteins in Relation to Blood Hydration, J. Clin. Investigation **11**:103, 1932.

17. Herrmann, G.: Some Blood Chemical Findings in Congestive Heart Failure Before and After Treatment, South. M. J. **25**:934, 1932.

18. Govaerts, P.: Influence de la teneur du sérum en albumines et en globulines sur la pression osmotique des protéines et sur la formation des oedèmes, Bull. Acad. roy. de méd. de Belgique **7**:356, 1927.

blood cell and plasma protein values. For example, in patients recovering from mild heart failure, especially those with failure purely of the left side of the heart, it is often impossible to detect an appreciable change in plasma volume by this method. Secondly, the method is applicable only when the change in volume is extremely rapid, taking place within a few days. When the change occurs slowly, over weeks or months, time is allowed for complicating factors to appear which may alter the red blood cell count and plasma protein concentration directly, making interpretation of the changes in relation to plasma volume unreliable. Fortunately, a more accurate dye method has recently been perfected [19] from which the sources of error inherent in the older dye methods have been eliminated. It is to be hoped that the application of this method to the study of cardiac insufficiency will result in more accurate data on plasma volume [20] and will lead to a clearer understanding of this important phase of the pathologic physiology of congestive heart failure.

SUMMARY

Appreciable increases in the volume of packed red blood cells, hemoglobin value, red blood cell count and plasma protein concentration have been observed for patients during recovery from severe congestive heart failure. These changes take place rapidly, within three to six days, and are interpreted as indicating a decrease in the volume of plasma. The possible relation between the decrease in plasma volume and the disappearance of cardiac edema is discussed.

19. Gregersen, Gibson and Stead.[81] Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method of Employing the Azo Dye "Evans Blue" and the Spectrophotometer, J. Clin. Investigation **16**:301, 1937.

20. Since this paper was written an excellent study of the changes in the blood volume in congestive heart failure by the more accurate dye method has been published, confirming the observations here reported (Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: III. Changes in Blood Volume, Venous Pressure and Blood Velocity Rate in Chronic Congestive Heart Failure, J. Clin. Investigation **16**:851, 1937).

Progress in Internal Medicine

RECENT ADVANCES IN KNOWLEDGE OF THE ANTERIOR LOBE OF THE HYPOPHYSIS

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In this, the first report on this subject to appear in the ARCHIVES OF INTERNAL MEDICINE, we wish to state the limitations we have imposed and the objective which we have set. We are not attempting a detailed review of the established knowledge in this field. This can be obtained from many volumes.[1] Nor shall we attempt to quote all the pertinent literature. Abstracts may be found in the current numbers of *Endocrinology* and in the excellent annual review written by Elmer Sevringhaus in "The Year Book of Neurology, Psychiatry and Endocrinology."[2] The present report is not being written by or for those who are actively engaged in fundamental work in this field. Laboratory workers will find it inadequate for their purpose. It is not being written by or for those who specialize in "endocrinology."

Our aim is to record the important relations of the anterior lobe of the hypophysis for those who, like ourselves, are practicing internal

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1. (*a*) Allen, E.: Sex and Internal Secretions: A Survey of Recent Research, Baltimore, Williams & Wilkins Company, 1932. (*b*) Kurzrok, R.: The Endocrines in Obstetrics and Gynecology, Baltimore, Williams & Wilkins Company, 1937. (*c*) Mazer, C., and Goldstein, L.: Clinical Endocrinology of the Female, Philadelphia, W. B. Saunders Company, 1932. (*d*) Glandular Physiology and Therapy, Chicago, American Medical Association, 1935. (*e*) Rolleston, H. D.: The Endocrine Organs in Health and Disease, with an Historical Review, New York, Oxford University Press, 1936. (*f*) Cameron, A. T.: Recent Advances in Endocrinology, ed. 1, Philadelphia, P. Blakiston's Son & Co., 1934; ed. 3, London, J. & A. Churchill, Ltd., 1936. (*g*) Van Dyke, H. B.: The Physiology and Pharmacology of the Pituitary Body, Chicago, University of Chicago Press, 1936. (*h*) The Pituitary Gland: An Investigation of the Most Recent Advances, Association for Research in Nervous and Mental Disease, Baltimore, Williams & Wilkins Company, 1938, vol. 17. (*i*) Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, Long Island, New York, The Biological Laboratory, 1937, vol. 5.

2. Sevringhaus, E. L.: Endocrinology: The Year Book of Neurology, Psychiatry and Endocrinology, Chicago, The Year Book Publishers, Inc., 1937.

medicine, in the broader sense of the term. In doing this we have attempted to refer to only a few "key" sources from which extensive bibliographic references may be obtained; the bibliography for this article is therefore limited.

Most of the hormonal substances which have proved of value in clinical medicine have been obtained from organs such as the pancreas, thyroid gland, sex glands and adrenal glands, rather than from the anterior lobe of the hypophysis, which has an effect on all of them. Since we are discussing only the hormones of the anterior lobe of the hypophysis, we must omit mention of androgens and estrogens and certain other glandular factors. Finally, we are reporting largely the accepted findings of the laboratory. The clinical application of these findings is incomplete and cannot be judged.

For many years knowledge of the anterior lobe of the hypophysis was limited to that obtained from a study of its anatomy, histology, cytology and pathology. The cytologists taught that there are three types of cells: chromophobe cells, which have no generally accepted secretory function; eosinophilic cells (a tumor of which produces acromegaly or gigantism), and basophilic cells (a tumor of which was later found by Cushing to produce the syndrome which carries his name). A new era really began when Evans and Long [3] reported their work with the growth hormone in 1921. In the intervening seventeen years thousands of articles have reported work on the many hormones, real or suspected, which are attributed to the anterior lobe of the hypophysis. Separate hormones have been reported to have an effect on growth; lactation; behavior; blood; pigmentation; metabolism of carbohydrate, protein, fat and water; production of ketone bodies, and activity of the thyroid, parathyroid, pancreas, adrenal and sex glands—and this list is incomplete. When incomplete knowledge of these effects reached the ears of some indiscriminating and overly enthusiastic clinicians, there followed the publication of many more "contributions" to medical literature. It is only within recent years that a semblance of order has developed.

Even now it is not known how many hormones are produced by the anterior lobe of the hypophysis, and most certainly the clinical application of most of them is not understood. It is inconceivable that two secreting cells can produce all the hormones which have been reported. This does not mean that the anterior lobe of the hypophysis does not have many effects on the body and its metabolic processes; it indicates, rather, that these effects probably will be explained with fewer hormones

3. Evans, H. M., and Long, J. A.: The Effect of Feeding the Anterior Lobe of the Hypophysis on the Oestrous Cycle of the Rat, Anat. Rec. **21**:62 (April) 1921.

than are required at present. Certain cytologists, notably Rasmussen [4] and Aura Severinghaus,[5] have offered much help. The recent studies of Severinghaus considered not only the cytology of pituitary tumors but the cytologic changes which are associated with such diseases as hypertension, nephritis, Addison's disease, tumors of the brain, diseases associated with castration and pregnancy, diseases which follow the injection of various preparations containing androgens and estrogens and those which follow thyroidectomy and artificial hyperthyroidism. In the summary he said:

> Growth phenomena as seen in acromegaly and in the dwarf mice are unquestionably related to the acidophile cells. In pregnancy both the acidophiles and basophiles actively secrete. They are then jointly concerned with the reproductive phenomena involved in the pregnant state. Castration, likewise, has its effect on both cell types, although the increase of basophiles seems the more prominent alteration. This increase is associated with greater gonad-stimulating potency, and has, therefore, linked the basophile to the production of the hormone involved. It is almost certain, however, that two gonad-stimulating hormones are elaborated, and there is evidence to indicate that the acidophile may also be a source of one of these. Injections of pregnancy urine and of gonadal hormones, likewise, have their effect on both granular types of cells, although males and females do not respond similarly to all injections. This is additional evidence that both cells take part in the hypophysial control of gonad activity. Thyroidectomy and thyroid administration, likewise, affect both granular cells, and in some respects these effects are not unlike those produced by disturbances in the gonadal relationship. This not only indicates that we may not yet eliminate either cell type from thyroid relationship but it emphasizes the necessity of further study of thyroid gonadal relationships and their joint reactions with the anterior hypophysis. One should like to give way to over optimism or enthusiasm and say that with the rapid advances of experimental and cytologic researches during the last few years, the time will not be far distant when we can speak with certainty of the hormones of the anterior lobe and the cells responsible for their elaboration. When that day comes, the cytologist, at least, expects that the number of anterior lobe hormones will be much fewer than it is today, and that the varying responses of the organism will be interpreted as individual reactions to a given hormone rather than responses to individual hormones.

THE MAMMOTROPIC OR LACTOGENIC HORMONE

The rapid advance in knowledge of lactation can be illustrated by the statement that any animal equipped with nipples, whether male or

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4. Rasmussen, A. T.: The Proportions of the Various Subdivisions of the Normal Adult Human Hypophysis Cerebri and the Relative Number of the Different Types of Cells in Pars Distalis, with Biometric Evaluation of Age and Sex Differences and Special Consideration of Basophilic Invasion into the Infundibular Process, A. Research Nerv. & Ment. Dis., Proc. **17**:118-150, 1938.

5. Severinghaus, A. E.: The Cytology of the Pituitary Gland, A. Research Nerv. & Mental Dis., Proc. **17**:69-117, 1938; Some Aspects of Anterior Lobe Function, Suggested by a Cytological Analysis of Experimentally Altered Glands, in Cold Spring Harbor Symposia on Quantitative Biology,[11] pp. 145-150.

female, can be made to lactate. This statement is startling in more ways than one, for it suggests that in the near future fatherhood may not be so simple!

Lactation is not the effect of a single hormone. Students of this particular problem may disagree with this brief summary, but in general it may be stated that the process occurs about as follows: First, the breast must be stimulated by estrogen. Without this influence no other steps are possible. Second, in all probability the hormone of the corpus luteum further aids in the development of the breast. Nelson [6] has emphasized the important role of the corpus luteum. Lyons' [7] somewhat conflicting opinions can be found in his recent summary. Third, the lactogenic hormone initiates lactation; lactation is impossible without this stimulus.

Thus, in the human being development of the breast never occurs until the ovaries are functioning. Precocious development of the breasts always indicates the presence of prematurely functioning ovaries. Changes which occur in the breasts during menstruation are further evidence of the close relation which exists between the pituitary body, the ovaries and the breasts. During pregnancy a large amount of estrogen is produced; this increases the development of the breasts and opposes the production of the lactogenic hormone by the pituitary body. The sudden loss of estrogen when the placenta is expelled releases the lactogenic hormone, and lactation is initiated.

No one knows how many other glands may be indirectly concerned with the physiology of lactation. Nelson and Gaunt [8] have enlarged on their original observation that the lactogenic hormone alone cannot initiate lactation in a hypophysectomized guinea pig; it must be combined with the hormone of the adrenal cortex. Any studies of the relation of the adrenal glands to the development of the breast and lactation are of interest to those physicians who are often puzzled by the changes in the breasts that occur in association with tumors of the adrenal glands.

Riddle and Bates [9] and their associates at Cold Spring Harbor have

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6. Nelson, W. O.: Studies on the Physiology of Lactation: IV. The Assay of the Lactogenic Hormone of the Anterior Hypophysis, Anat. Rec. **60**:69-76 (Aug.) 1934.

7. Lyons, W. R.: The Preparation and Assay of Mammotropin, in Cold Spring Harbor Symposia on Quantitative Biology,[11] pp. 198-209.

8. Nelson, W. O., and Gaunt, R.: Initiation of Lactation in the Hypophysectomized Guinea Pig, Proc. Soc. Exper. Biol. & Med. **34**:671-673 (June) 1936; The Adrenals and Pituitary in Initiation of Lactation, ibid. **36**:136-138 (March) 1937.

9. Riddle, O., and Bates, R. W.: Prolactin, A. Research Nerv. & Ment. Dis., Proc. **17**:287-297, 1938. Riddle, O.: Physiological Responses to Prolactin, in Cold Spring Harbor Symposia on Quantitative Biology,[11] pp. 218-228.

studied the lactogenic hormone for many years, and their list of achievements is impressive. In two recent articles Riddle reviewed his changing conceptions regarding this hormone. Originally, it was assumed to have only lactogenic and crop sac–stimulating effects. Now it is suggested that this hormone is concerned also with increasing the basal metabolic rate, that it has an "antigonad" action, that it generates the brooding instinct in fowl and seems capable of inducing maternal behavior in virgin rats, that it produces splanchnomegalia and increases bodily growth and that it is concerned with the metabolism of carbohydrate and fat. Needless to say, such a conception has aroused controversy, particularly when it raises doubts regarding the existence of the oldest and best established hormone, the growth hormone. Riddle expressed the opinion that too many hormones have been suggested. He said:

> Much confusion has arisen in the field of pituitary physiology because too often it has been assumed that a newly observed response means a new pituitary hormone; and thereafter, instead of speaking of this response, the name of an alleged hormone has been used. In our opinion very few anterior lobe hormones have been adequately established, though it is granted that hereafter others may attain that status. But to date our diligence has been rewarded with no opportunity to examine a physiologically active preparation from anterior pituitary tissue (excluding intermedin) which did not contain effective amounts of follicle stimulating hormone, thyrotropic hormone, or prolactin; if adrenotropin is an entity, it probably could be added to this list.

The opinion of a disinterested observer might be that Riddle has not eliminated the confusion attendant on multiple hormones; he has simply transferred all the confusion to one hormone, the lactogenic hormone.

Some of this confusion may be cleared since White, Catchpole and Long [10] have announced that by following the method of Lyons they have produced a crystalline protein from the pituitary body and that this protein possesses "high lactogenic activity." This is the first report of the crystallization of any hormone of the anterior lobe of the hypophysis.

The literature regarding the clinical application of this hormone is not impressive. Most reports are valueless. Kurzrok and his associates,[11] who administered a preparation containing the lactogenic hormone to 29 patients whose supply of milk was inadequate, noted an increased production of milk in 25 instances.

Lyons [12] has described a method for assaying the amount of lactation-stimulating principle by the simple method of injecting unconcentrated

10. White, A.; Catchpole, H. R., and Long, C. N. H.: Crystalline Protein with High Lactogenic Activity, Science **86**:82-83 (July 23) 1937.

11. Kurzrok, R.; Bates, R. W.; Riddle, O., and Miller, E. G., Jr.: The Clinical Use of Prolactin, Endocrinology **18**:18-19 (Jan.-Feb.) 1934.

12. Lyons, W. R.: Preparation and Assay of Mammotropic Hormone, Proc. Soc. Exper. Biol. & Med. **35**:645-648 (Jan.) 1937.

urine subcutaneously into pigeons and observing the effect on the crop glands. It is to be hoped that this test will receive wide clinical trial. The patient's urine should be subjected to this test before it is concluded that the insufficiency of the supply of milk is due to a deficiency of lactogenic hormone.

THE DIABETOGENIC HORMONE

Physicians who treat large numbers of diabetic patients are impressed with the different forms of the disease. Diabetes in a child may appear suddenly, may be severe and may be difficult to control. The mild diabetes which may be noted in the child's grandfather is as different as if it were an entirely different disease, yet both patients have diabetes. The diabetes which sometimes is associated with cerebral hemorrhage responds to the same treatment as does any other type of diabetes.

These differences and the association of diabetes with diseases of other endocrine glands have led many physicians to believe that diabetes may have multiple etiologic factors. Others believe in a unitarian cause, the lack of insulin; this belief has been recently reviewed by Wilder.[13]

The frequent association of diabetes and acromegaly has focused attention on the anterior lobe of the hypophysis. (We shall not consider the posterior lobe, although the hyperglycemic effect of pitressin is well known.) The investigator who more than any other has contributed to the knowledge of the relation of the anterior lobe of the hypophysis to carbohydrate metabolism is B. A. Houssay, professor of physiology at the University of Buenos Aires. He and his associates have reported in numerous papers the exhaustive work in progress in his laboratory. He has reported on this work in English in two rather recent articles.[14] In the more recent of these he related his observations on the pituitary-carbohydrate relation to the whole problem of diabetes. He discussed the important correlation of many endocrine glands in carbohydrate metabolism—pituitary body, pancreas, adrenal glands (both the cortex and the medulla), thyroid gland and gonads.

His own contributions to the study of the important role of the anterior lobe of the hypophysis were given in more detail in the Dunham Lectures, delivered at Harvard University in 1935. He summarized his findings by stating:

> Our experimental work has shown: (1) In the absence of the pituitary (or of the anterior lobe) pancreatic and phlorizin diabetes is attenuated and animals retain and consume glucose. (2) Anterior pituitary lobe extract counteracts

13. Wilder, R. M.: The Etiology of Diabetes, J. Med. **18**:275-282 (Aug.) 1937.

14. Houssay, B. A.: Diabetes as a Disturbance of Endocrine Regulation, Am. J. M. Sc. **193**:581-606 (May) 1937; Carbohydrate Metabolism, New England J. Med. **214**:971-986 (May 14) 1936.

the action of insulin, increases pancreatic and phlorizin diabetes . . . (3) Anterior pituitary extract can produce diabetes in normal mammals. (4) When the pituitary is absent there is a tendency to hypoglycemia, hypersensitivity to insulin and other hypoglycemic agents . . .

It is impossible to discuss Houssay's work without mentioning the work of Long and Lukens, a complete report of which is to be found in the Harvey Lectures of 1937.[15] The relation of the adrenal glands to carbohydrate metabolism is not properly a part of our subject, but brief mention of this relation must be made. Long and Lukens demonstrated that removal of the adrenal cortex was followed by changes in the metabolism of carbohydrate which are every bit as striking as those produced by hypophysectomy and are similar in many respects. Furthermore, they demonstrated that in the absence of the adrenal cortex there was no diabetogenic effect after the injection of anterior pituitary extracts. Their reports have led to an interesting exchange of opinions with Houssay. A disinterested observer is impressed with the excellent work of both laboratories. There can be no doubt of the importance of the adrenal cortex in the intricate metabolism of carbohydrate. Long has finally been able to answer the last criticism of his work by producing hyperglycemia with an extract of the adrenal cortex that was supplied by Kendall. It is regrettable that space prevents a more detailed summary of the work of Houssay and of Long and Lukens.

A most complete summary of this entire problem by one who is strictly impartial recently appeared. In this article Russell[16] discussed not only the findings of workers in this field but the theories behind such findings. In her summary she said:

Two principal theories have been advanced in explanation of these and related findings—one, that the anterior lobe controls gluconeogenesis from endogenous protein, if not from fat, administration of its extract causing an increase in available glucose and its removal curtailing the supply; the other theory, that the anterior lobe influences carbohydrate oxidation itself, its presence preventing carbohydrate loss below certain levels and its absence characterized by lack of restraint on carbohydrate oxidation under conditions when such would ordinarily occur. Although this reviewer inclines to the latter explanation, at present it is not possible to make a final decision as to the validity or completeness of either of these theories.

The final reference is to work which is of far reaching importance. Young[17] has been able to produce permanent diabetes in dogs after

15. Long, C. N. H.: The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, pp. 194-228; Medicine **16**:215-247 (Sept.) 1937.

16. Russell, J. A.: The Relation of the Anterior Pituitary to Carbohydrate Metabolism, Physiol. Rev. **18**:1-27 (Jan.) 1938.

17. Young, F. G.: Permanent Experimental Diabetes Produced by Pituitary (Anterior Lobe) Injections, Lancet **2**:372-374 (Aug. 14) 1937.

injection of an anterior pituitary extract. Recent confirmation of this work was reported by Campbell and Best,[18] who said:

> After the report by F. G. Young that what appeared to be a permanent diabetes may be produced in dogs by the intraperitoneal injection of certain extracts of the anterior pituitary gland, similar experiments were initiated in this department. Our findings are in accord with those reported by Young. Some of the animals failed to respond, in that diabetes did not appear. In one, a mild but constant glycosuria persisted after discontinuing the injections of the extract; in another, the sugar excretion was most irregular. In a third, an intense glycosuria persisted for a prolonged period and showed no signs of abatement. This animal was no more resistant to insulin than the average depancreatized dog. The findings with regard to the sugar excretion and sensitivity to insulin will be reported in some detail.

The importance of this accomplishment to clinical medicine is obvious, for there are many hypoglycemic states which conceivably may be due to a lack of the diabetogenic or "blood sugar raising" principle. At present no such extract is available for clinical trial.

Study of the diabetogenic hormone is interesting and important, but it should not encourage any one to abandon the accepted and successful methods of treating diabetes mellitus. One physician who has been treating diabetes and hypertension by the application of roentgen rays to the pituitary body concluded an article by saying: "There is so little evidence to support the pancreatic theory of diabetes that it should be discarded . . ." Further comment is unnecessary.

HORMONES AFFECTING THE METABOLISM OF PROTEIN AND FAT

No special discussion will be made of these "hormones," for there is insufficient evidence that individual hormones of this type exist. It is true that during the course of studies which have been referred to there is ample evidence of an effect not only on the metabolism of carbohydrate but on the metabolism of protein and fat as well. It does not logically follow that this indicates the effect of a specific hormone. The numerous papers of Anselmino and Hoffman, in which they reported the isolation of many specific metabolic hormones, including a fat metabolism or ketogenic hormone, have not received general confirmation. Thomson[19] has reviewed the work on the ketogenic hormone which was done in the laboratory. He expressed the opinion that much of it will need repetition.

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18. Campbell, J., and Best, C. H.: Prolonged Diabetes After Administration of Extracts of the Anterior Pituitary Gland, paper presented at the meeting of the American Physiological Society, March 30-April 2, 1938.

19. Thomson, D. L.: The Anterior Pituitary and the Metabolism of Acetone Bodies, A. Research Nerv. & Ment. Dis., Proc. **17**:257-267, 1938.

THYROTROPIC HORMONE

The elevation of the basal metabolic rate in cases of acromegaly and its depression in cases of pituitary insufficiency have for some time suggested the presence of some hormone of the anterior lobe of the hypophysis which has an effect on and through the thyroid gland. It was hoped that such a hormone would be of value in treating certain patients who have low basal metabolic rates with or without myxedema. A review of the literature does not disclose the fulfilment of this hope. Scowen [20] has published an excellent article in which he proved for human beings what had been found true in experiments on animals—that the thyrotropic hormone can be expected to be of value only when the thyroid gland is normal and that it is therefore of no clinical value in cases of myxedema. Thyroid is, and probably will remain, the most effective, most easily administered and cheapest form of medicament for this disease. Scowen described the elevation of the basal metabolic rate in normal persons after the injection of a pituitary preparation containing the thyrotropic hormone and reported his ability to raise the basal metabolic rate of patients whose low rate he suspected was due to lack of thyrotropic hormone. When Collip and Anderson [21] announced the production of an antithyrotropic serum, further hope was expressed that this substance might be of help in treating patients suffering from hyperthyroidism. This hope also has remained unfulfilled.

Uhlenhuth [22] has written a thorough review of the observations made by him and others on the relation of the thyrotropic hormone to the cytology of the thyroid gland. This paper, awarded the Van Meter Prize by the American Association for the Study of Goiter, reported some interesting studies. Starr and Rawson [23] have described a quantitative method of measuring the effect of the thyrotropic hormone (the preparation administered was antuitrin-T) by measurement of the height of the acinar cells of the thyroid gland.

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20. Scowen, E. F.: Effects of the Thyrotropic Hormone of the Anterior Pituitary in Man, Lancet **2**:799-802 (Oct. 2) 1937.

21. Collip, J. B., and Anderson, E. M.: The Production of Serum Inhibitory to the Thyrotropic Hormone, Lancet **1**:76-78 (Jan. 13) 1934; Studies on the Thyrotropic Hormone of the Anterior Pituitary, J. A. M. A. **104**:965-969 (March 23) 1935.

22. Uhlenhuth, E.: The Thyreoactivator Hormone: Its Isolation from the Anterior Lobe of the Bovine Pituitary Gland and Its Effects on the Thyroid Gland, Ann. Int. Med. **10**:1459-1486 (April) 1937; Tr. Am. A. Study of Goiter, 1936, pp. 25-50.

23. Starr, P., and Rawson, R. W.: A Graphic Representation of Thyroid Response to Stimulation by Thyrotropic Hormone, Proc. Soc. Exper. Biol. & Med. **35**:603-605 (Jan.) 1937. Rawson, R. W., and Starr, P.: Direct Measurement of Height of the Thyroid Epithelium: A Method of Assay of Thyrotropic Substance; Clinical Application, Arch. Int. Med. **61**:726-738 (May) 1938.

The opportunity to measure, by this or other methods, the amount of thyrotropic hormone which is present in different metabolic conditions should produce some interesting data. It is hoped that such studies may prove of help in the management of such puzzling conditions as the exophthalmos which progresses after thyroidectomy, recurrent exophthalmic goiter and a low basal metabolic state without myxedema.

PARATHYROTROPIC HORMONE

Not much is being written about this hormone; there are many who doubt the existence of a specific parathyrotropic hormone. Riddle and Dotti [24] performed some interesting experiments which seemed to throw doubt on the existence of a specific parathyrotropic hormone but which indicated some hormonal control of calcium metabolism. They found that the prolonged administration of an adequate amount of gonadotropic substance caused an increase in the amount of calcium in the serum of normal, hypophysectomized or thyroidectomized pigeons but did not have this effect when injected into castrated pigeons.

THE ADRENOTROPIC HORMONE

There really is not much to be said about this hormone, if it is a separate hormone. It is known only that the adrenal glands, in common with all other glands of internal secretion, undergo atrophy after hypophysectomy and that they can be somewhat restored by the injection of "adrenotropic hormone," which may or may not be related to the lactogenic hormone. Until purification, if possible, is complete, this hormone cannot be studied properly either in animals or in man. Gaunt [25] has reviewed this subject. It is evident that further work should include a detailed study of the effect of this hormone on the metabolism of the blood electrolytes, which are so typically abnormal in most cases of Addison's disease.

THE ANTERIOR LOBE OF THE HYPOPHYSIS AND WATER METABOLISM

The important relation between the posterior lobe of the hypophysis and water metabolism has long been known and has received wide clinical application in the use of pitressin in the treatment of diabetes insipidus. At the Institute of Neurology of Northwestern University Medical School, Ranson and his associates have done outstanding work in studying experimentally induced diabetes insipidus. The results of this work

24. Riddle, O., and Dotti, L. B.: Blood Calcium in Relation to Anterior Pituitary and Sex Hormones, Science **84**:557-559 (Dec. 18) 1936.

25. Gaunt, R.: The Adrenal-Pituitary Relationship, in Cold Spring Harbor Symposia on Quantitative Biology,[11] pp. 395-404.

have recently been published.[26] A summary may be found in Ingram's article.[27] The important hypothalamic mechanisms which affect water metabolism are described.

Richter [28] has reviewed his studies on water metabolism, which have centered about the role of the anterior lobe of the hypophysis in the production of diabetes insipidus. He found that the only way permanent diabetes insipidus can be produced is by allowing the anterior lobe of the hypophysis to remain. His summary was as follows:

1. In the rat, production of diabetes insipidus depends on the removal of the anti-diuretic hormone, pituitrin, secreted by the posterior lobe.

2. The syndrome can be produced (1) by total hypophysectomy; (2) by stalk section near the brain; (3) by posterior lobectomy.

3. The permanency of the symptoms depends on the presence of anterior lobe tissue and the maintenance of normal metabolism. The symptoms are never permanent when all anterior lobe tissue is removed.

4. The role played by the intermediate lobe has not been definitely determined.

5. Polyuria is primary; polydipsia secondary.

6. The maximum diuresis of diabetes insipidus is as great as the maximum diuresis produced by forcing fluids. It is limited probably by the maximum capacity of the kidneys.

It can be concluded that production of diabetes insipidus depends on the removal of the secretion from the posterior lobe and possibly the intermediate lobe. The removal of this hormone which normally controls the secretion of urine, causes a marked diuresis. This resulting dehydration in time produces drying of all membranes including those of the throat, which gives rise to an increased thirst, and an increased water intake. The permanency of the increase of urine output and water-intake is dependent on the maintenance of normal metabolism as governed by secretion from the anterior lobe.

This work was confirmed in its essential details by Pencharz, Hopper and Rynearson.[29]

THE GONADOTROPIC HORMONES

A few years ago rapid advances were made in the knowledge of the relation of the anterior lobe of the hypophysis to the sex glands.

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26. Fisher, C.; Ingram, W. R., and Ranson, S. W.: Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance: A Contribution to the Structure and Function of the Hypothalamico-Hypophyseal System, Ann Arbor, Mich., Edwards Brothers, Inc., 1938.

27. Ingram, W. R.: The Relation of the Hypophysis and Associated Hypothalamic Mechanisms to Water Exchange, in Cold Spring Harbor Symposia on Quantitative Biology,[11] pp. 381-394.

28. Richter, C. P.: The Pituitary Gland in Relation to Water Exchange, A. Research Nerv. & Ment. Dis., Proc. **17**:392-409, 1938.

29. Pencharz, R. I.; Hopper, J., Jr., and Rynearson, E. H.: Water Metabolism of the Rat Following Removal of the Anterior Lobe of the Hypophysis, Proc. Soc. Exper. Biol. & Med. **34**:14-17 (Feb.) 1936.

Briefly, knowledge was obtained of at least two gonadotropic hormones —one which was believed to be primarily follicle stimulating and one which was primarily luteinizing. A third hormone, a synergist, was described but is now rarely mentioned. The term synergism continues to apply, however, to the action which follows the injection of both the follicle-stimulating and the luteinizing fraction.

Equally serious study was given to hormones obtainable from the blood and urine of human beings and animals. Again, two hormones were found. One had a follicle-stimulating effect; it was easily obtained from the urine of castrated persons and of women past the menopause and is even now believed to be a true pituitary hormone. The other, obtained from the urine of pregnant women, from the placenta and from the blood of pregnant mares, had a luteinizing effect, and while originally it was believed to have its origin in the pituitary body, it was soon proved to be a product of the chorionic villi.

At about the same time, rapid advances were being made in studying the hormones of both the male and the female sex glands. Physicians then had preparations containing both pituitary and sex gland hormones for clinical trial, and the medical literature of that period records the beginning of the hectic race which was run, with both laboratory workers and clinicians competing. The officials of pharmaceutic houses were at their wits' ends. Here was a new field, and they were not going to be "left out." And so with laboratory workers competing for priority and with clinicians injecting large quantities of hormonal preparations of one type or another into patients suffering from a variety of conditions, the race was on. It is not over yet, but at least some laboratory workers and clinicians are beginning to slow down a little so as to catch their "second wind" and see how far they have come.

The volumes mentioned at the beginning of this article contain much helpful material, particularly the most recent publications. The best work, from the standpoint of its clinical value, lies in the field of the male and female sex glands and is not a part of this subject.

The "sex hormones" of the anterior lobe of the hypophysis are still believed to be the follicle-stimulating hormone (which also affects the germinal cells in the male) and the luteinizing hormone (which also affects the interstitial cells and the accessory sex glands in the male). Fevold,[30] who has done outstanding work in this field, has reviewed the subject and has defended the belief that there are two hormones. This defense has been necessary because of the belief in some quarters that there is only one gonadotropic hormone, that the different effects reported for the two hormones represent a quantitative and not a quali-

30. Hisaw, F. L.; Fevold, H. L., and Greep, R. O.: The Pituitary Gonadotropic Hormones, A. Research Nerv. & Ment. Dis., Proc. **17**:247-256, 1938.

tative difference and that if enough follicle-stimulating hormone is given, luteinization will follow. It is too early to evaluate the recent announcement by Evans, Simpson and Pencharz [31] of a third hormone, "the interstitial cell–stimulating hormone."

Whether there are one, two or three pituitary gonadotropic hormones, the fact remains that none of them has been given an adequate clinical trial. By this we mean that there is, at present, no available commercial preparation which can be recommended as containing uncontaminated gonadotropic hormones. Our authorities are Fevold [32] and Fluhmann.[33] If one does not have the hormone, then surely one cannot test it; yet there are numerous articles reporting treatment with "pituitary gonadotropic hormones." Of course what is usually meant by this term is a "pituitary-like gonadotropic substance" obtained from the urine, blood or placenta of pregnant women or animals. As stated previously, this is *not* of pituitary origin. We shall appreciate correction, but we are not familiar with any commercial preparation of the gonadotropic substance in the urine of castrated subjects or of women who are past the menopause, which, as mentioned before, is almost certainly of pituitary origin.

Therefore, at this "lull in the race" we should like to suggest that if clinicians are to be expected to test pituitary gonadotropic hormones, they should be given some pure ones to use and that until they have them they cease reporting results in which they use this term. This statement does not mean that hormonal preparations obtained from other sources are not of value and should not be used; it is simply a plea for more accurate description of the material used. The "chorionic hormone" is of value in many conditions; it is not a pituitary hormone.

We cannot discuss here the many important uses of the gonadotropic hormones, except to make a plea that conservatism be used in this field as well. A few years ago the literature was crowded with reports of "100 per cent cure" of this and that. It simply was not so. Nothing is 100 per cent, and when some one reports descent of the testes within twenty minutes of the time of injection of the hormonal preparation, it means one thing only—that the testes were not "undescended" in the first place. Such conservative reports as those published in a symposium

31. Evans, H. M.; Simpson, M. E., and Pencharz, R. I.: An Anterior Pituitary Gonadotropic Fraction (ICSH) Specifically Stimulating the Interstitial Tissue of Testis and Ovary, in Cold Spring Harbor Symposia on Quantitative Biology,[11] pp. 229-240.

32. Fevold, H. L.: The Gonadotropic Hormones, in Cold Spring Harbor Symposia on Quantitative Biology,[11] pp. 93-103.

33. Fluhmann, C. F.: Biologic Differences Between Anterior Pituitary Sex Hormones and Gonadotropic Substances from Pregnant Women, A. Research Nerv. & Ment. Dis., Proc. **17**:350-360, 1938.

in 1937 [34] should be reread. Less well considered material should not be published.

THE GROWTH HORMONE

The growth hormone is being discussed last because it was discovered first, because it is the only pituitary hormone which has received extensive clinical trial and because its very existence recently has been questioned. Riddle,[35] as mentioned in the discussion of lactogenic hormone, stated the opinion that there is no growth hormone and that the growth effect is produced by a combination of lactogenic and thyrotropic hormones. His presentation of this conception has already been referred to.

Evans [36] has presented his answer, and many physicians will wish to read his spirited reply in its entirety. There is space for only two quotations:

> I now propose to test in five different ways the concept that the growth hormone is merely a mixture in certain proportions of lactogenic and thyrotropic hormones:
>
> 1. Growth hormone has been prepared remarkably high in its growth promoting values and remarkably low in the above hormones.
>
> 2. A very considerable number of hypophyseal extracts containing recognizable amounts of lactogenic and thyrotropic hormones have been studied with reference to the growth produced by them and to the quantitative relations of these two hormones. The growth effect cannot be shown to run parallel with the content of lactogenic and thyrotropic hormones or with any ratio between these two.
>
> 3. Combinations of thyrotropic and lactogenic hormones in the amounts actually present in impure but potent growth extracts produce only minimal, if any, growth effects on hypophysectiomized mammals.
>
> 4. Thyrotropic and lactogenic extracts containing low but recognizable amounts of growth hormone have been administered at such high levels as to produce

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34. Frank, R. T.; Goldberger, M. A.; Salmon, U. J., and Felshin, G.: Amenorrhea: Its Causation and Treatment, J. A. M. A. **109**:1863-1869 (Dec. 4) 1937. Burch, J. C.; McClellan, G. S.; Simpson, J. W.; Johnson, C. D., and Ellison, E. T.: The Treatment of Menorrhagia and Metrorrhagia by Endocrine Products, ibid. **109**:1869-1871 (Dec. 4) 1937. Litzenberg, J. C.: The Endocrines in Relation to Sterility and Abortion, ibid. **109**: 1871-1873 (Dec. 4) 1937. Lewis, R. M., and Adler, E. L.: Endocrine Treatment of Vaginitis of Children and of Women After the Menopause, ibid. **109**:1873-1875 (Dec. 4) 1937. Pratt, J. P., and Thomas, W. L.: The Endocrine Treatment of Menopausal Phenomena, ibid. **109**:1875-1877 (Dec. 4) 1937. Abstract of discussion on papers by Frank and others, Burch and others, Litzenberg, Lewis and Adler, and Pratt and Thomas, ibid. **109**:1877-1880 (Dec. 4) 1937.

35. Riddle, O.: Physiological Responses to Prolactin, in Cold Spring Harbor Symposia on Quantitative Biology,[11] pp. 218-228.

36. Evans, H. M.: The Hypophyseal Growth Hormone—Its Separation from the Hormones Stimulating the Thyroid, Gonads, Adrenal Cortex and Mammary Glands, A. Research Nerv. & Ment. Dis., Proc. **17**:175-192, 1938.

slight growth. Under these circumstances, a synergic action on growth of the two hormones, when administered together, could not be demonstrated.

5. Not only does the claimed synergism not exist, but there is no sound biological ground for belief in the necessity of the lactogenic and thyrotropic hormones for the growth process. Lactogenic preparations have now been prepared in our laboratory free of growth effects at exceedingly high levels; nor does the growth process demand thyrotropic hormone; indeed the thyroid itself may be removed, as well as the hypophysis, and excellent growth will result when growth hormone is administered to such thyroidectomized-hypophysectomized animals . . .

In conclusion, let me repeat the assertion of my friend, Dr. Oscar Riddle, "Though the concept of a growth hormone as an individual entity has been useful, it does not seem to be true." I trust that I have brought the facts we actually possess into better consonance with the demands of a "scientific conscience" by substituting for this assertion the following statements:

No known mixtures of the other recognized and specific hormones of the hypophysis have as yet produced the phenomenon of general body growth so readily evoked by certain pituitary extracts. Mixtures of two particular hormones which have been declared to be responsible unquestionably do not do so. Growth extracts have been produced which impart a maximal growth stimulus at levels exerting no other observable effect on specific organs such as the thyroid, adrenal, mammary glands and gonads. At very high levels of administration, the thyrotropic, adrenotropic, mammotropic and gonadotropic hormones are eventually demonstrable. These hormones are, however, quantitatively at levels which make it wholly improbable that they play an essential role in invoking growth or in determining the degree of growth. Yet even if a role were established for them, the facts as we now know them could not invalidate the conception of a growth hormone. They would have no more significance than the well known need of the body, for instance, for adequate quantities of certain vitamins for growth to result. No amount of these vitamins will reëstablish growth in an otherwise untreated hypophysectomized animal. Neither can such a creature grow with massive quantities of growth hormone if the essential vitamins be withdrawn from its diet. The number of extrinsic factors essential for growth is multiple. It is conceivable but not established that there is similar need for several intrinsic factors. There is indubitably one essential intrinsic factor—the endocrine substance known as the hypophyseal growth hormone.

In the discussion of this paper Riddle referred to additional studies which he felt that Evans had overlooked and which he believed offered convincing evidence that growth is produced by a combination of lactogenic and thyrotropic hormones. He then said:

Of course, the existence of an individual growth hormone would be very simply indicated if Dr. Evans could hand us a preparation of "growth hormone," with proved capacity to make various suitable animals grow, and which has neither lactogenic, adrenotropic nor thyrotropic substance in it (the presence of gonad-stimulating hormone would be of little consequence). Then perhaps tomorrow I could say, "Yes, growth hormone it is." Hitherto no one has presented us with such material.

To a "sideline observer" this discussion promises to be interesting.

There is no doubt that extracts containing the growth hormone have had an effect when injected into patients classified as "pituitary dwarfs." (As mentioned earlier, the growth hormone is the only pituitary hormone with which clinicians have had any considerable experience.) While it is true that it will add height to certain young dwarfs, there is no authenticated case on record in which a dwarf has ever been restored to normal height by the injection of any preparation of this hormone yet available.

ANTIHORMONES

The last statement leads to a brief discussion of antihormones. It must be brief, for Collip,[37] who first announced the presence of antihormones, has reviewed what is known of the entire subject in but four pages. He said, in introduction:

> I wish it were possible in this communication to give a final answer to the vexed question as to the exact nature and significance of the anti-hormones. Unfortunately it is impossible for me to do this, so I must be content with an expression of a point of view, together with a review of the recent literature on the subject. I feel that the anti-hormone theory as presented in March, 1934, has been entirely justified. It has been a strong directing force of the work in my own laboratory and it has been, like all theories that have been of value, a challenge to workers to devise and carry out experiments designed to verify or disprove them.
>
> Are the anti-hormones present in the blood and tissues of normal animals or are they reaction products resultant to the parenteral administration of hormone-containing extracts? When the correct answer to this question has been obtained, the problem of the anti-hormone will have been solved in large measure.
>
> The fact that inhibition of certain hormone reactions has been obtained in experimental test animals treated with the serum of certain patients is very strong evidence that the anti-hormone so demonstrated has occurred spontaneously in these individuals.
>
> It must be emphasized, however, that there are many pitfalls in such tests. Inhibition of a certain hormone effect may be nonspecific. The effect of the inhibitory substance may be greatly modified by the method of administration. In general it is best that the hormone and the suspected antagonist be mixed in vivo and not in vitro; the injections should be made separately and at different sites; adequate control with hormone treatment only and inhibiting agent only should be run.

Most of the critics of his conception of antihormones have felt that the antihormones are simply ordinary antibodies. Of this he said:

> That true antibodies are formed in most instances in which animals are treated chronically with anterior lobe extracts containing protein which must be foreign, since the extracts are of necessity in most cases made from the glands of another species, has been proved abundantly. I am, however, firmly convinced that the inhibition of either the gonadotropic or of the thyrotropic hormone by

37. Collip, J. B.: Anti-Hormones, A. Research Nerv. & Ment. Dis., Proc. **17**: 268-275, 1938.

the serum of animals rendered resistant to these hormones by prolonged treatment with unphysiologic doses is due to the presence of a true antagonizing hormone in addition to the true serological immune substance.

CONCLUSIONS

Physicians who attempt to maintain a conservative and critical approach to medicine have long been disturbed by two things: First, their friends in the laboratories have seemed able to do marvelous things with the administration of various extracts to animals, and yet when patients have been treated with these extracts the results have been disappointing. Second, their enthusiastic colleagues the endocrinologists have been reporting brilliant results in all sorts of conditions; even baldness has been "curable" with a "pituitary hormone."

Now the conservative physicians feel better, for they can see a change occurring. Conservatism may yet have its "inning" in a game in which enthusiasm has been predominant. Articles are now appearing in which it is admitted that not all fat boys have "Fröhlich's syndrome"; that a weight reduction regimen is needed more often than a syringeful of "hormone." Articles are also appearing in which many conditions described as "Simmond's disease" are correctly diagnosed as anorexia nervosa. Some writers are even stating that they do not know what is wrong with the patient.

After all, there are only a few clearcut syndromes resulting from disturbances of the anterior lobe of the hypophysis; these are dwarfism; acromegaly or gigantism; Fröhlich's syndrome; Cushing's syndrome, and, rarely, Simmond's disease (pituitary cachexia).

Advance will continue along two lines: First, it will be made in the laboratories. We have attempted to present some of the contributions (and confusion) to be found in the laboratory study of the anterior lobe of the hypophysis. This work is of fundamental importance, and it must be encouraged in every institution in which it is in progress. Second, advance will come from the scientific application of this knowledge to patients. Splendid results have been achieved, and physicians who have adequate knowledge of endocrine products should be encouraged to treat patients whom they can study carefully and observe closely. Advancement will be halted by the continued improper publication of the results of unplanned and mismanaged treatments of patients who received unidentified preparations for undiagnosed conditions.

News and Comment

American College of Physicians.—The Twenty-Third Annual Session of the American College of Physicians will be held in New Orleans, with general headquarters at the Municipal Auditorium, March 27 to 31, 1939.

Dr. William J. Kerr, of San Francisco, is president of the college and will have charge of the program of general scientific sessions. Dr. John H. Musser, of New Orleans, has been appointed general chairman of the session and will be in charge of the program of clinics and demonstrations in the hospitals and medical schools and of the program of round table discussions to be conducted at the headquarters.

International Goiter Conference.—The Third International Goiter Conference, under the auspices of the American Association for the Study of Goiter, will be held in Washington, D. C., Sept. 12 to 14, 1938.

The official language of the conference will be English. Interpreters will be furnished for papers read in other languages.

Papers and discussions delivered or read at the meetings are to be published in full in the form of transactions.

Physicians who desire to participate in the program are requested to submit titles to Dr. Allen Graham, 2020 East Ninety-third Street, Cleveland.

American Congress of Physical Therapy.—The seventeenth annual scientific and clinical session of the American Congress of Physical Therapy will be held cooperatively with the twenty-second annual convention of the American Occupational Therapy Association, Sept. 12 to 15, 1938, at the Palmer House, Chicago. Preceding these sessions, the congress will conduct an intensive instruction seminar in physical therapy for physicians and technicians, from September 7 to 10, inclusive.

The program of the convention proper will include numerous special features, a variety of papers and addresses, clinical conferences and round table talks, and there will be extensive scientific and technical exhibits.

The instruction seminar should prove of unusual interest to every one interested in the fundamentals and in the newer advances in physical therapy. The faculty will be comprised of experienced teachers and clinicians; every subject in the field of physical therapy will be covered. Information concerning the convention and the instruction seminar may be obtained by addressing the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago.

Book Reviews

By-Effects in Salvarsan Therapy and Their Prevention, with Special Reference to the Liver Function. By V. Genner. Translation from the Danish by Hans Anderson, M.D. Price, 22 kroner. Pp. 360. Copenhagen: Levin & Munksgaard, 1936.

The author, in a comprehensive and systematic study, has correlated the complications of treatment of syphilis as observed in 5,526 cases encountered in the outpatient clinic of the Rigshospital, Copenhagen, from 1913 to 1932.

The material is presented in three parts. The first part is based on 148 cases of arsphenamine erythema studied in regard to the time of onset (including Milian's ninth day erythema), the amount of medication and the relation to subsequent development of jaundice, albuminuria and arthralgia. Patch and intracutaneous tests were performed on half the patients who had had arsphenamine erythema. The results of subsequent treatment of these patients with arsphenamine or bismuth are discussed. In 125 cases jaundice developed. It usually was a late manifestation, occurring after only two or more courses of arsphenamine had been given. The relation between acute jaundice from arsphenamine and epidemic jaundice is emphasized. Distinction is made between the syphilitic factor, the medicamentotoxic factor and the infectious factors. Albuminuria was seen in 176 cases and was of more frequent occurrence after treatment with arsphenamine and mercury than after the newer treatment with arsphenamine and bismuth. On the other hand, involvement of the joints did not appear until bismuth therapy was introduced.

The second part of the book is concerned with 316 outpatients who were thoroughly studied regarding subjective by-effects during one or several series of treatments. The giving of arsphenamine in concentrated solution of dextrose did away with most of the acute subjective by-effects but did not prevent the later development of jaundice and hepatitis in certain cases. In the third part of the book, correlation is made between the by-effects of arsphenamine therapy and the results of two or more types of tests of hepatic function. These were performed on 316 outpatients and on 87 patients who were hospitalized. Evidence of hepatic damage usually appeared first only some time after an intensive course of arsphenamine, but milder degrees of hepatic damage also occurred after bismuth therapy. Genner, in his conclusions, writes that "it is practical by watching for the subjective by-effects and employing the functional liver tests to differentiate those patients who are intolerant to salvarsan and to plan for them a suitable individualized treatment, so that they too may go through the salvarsan therapy without serious or permanent injury."

The last 80 pages of the book consist of reports of 146 cases of arsphenamine erythema and 125 cases of arsphenamine jaundice, together with a set of 17 elaborate tables and an adequate and pertinent bibliography. This arrangement enables the author to carry out an orderly discussion of various subjects without interruption for statement of irrelevant details in the report of individual cases. He presents a wealth of statistical data, yet in such a way that the book is easy and pleasant to read.

The translation into English is especially well done. The observations and discussions presented are essentially in accord with those reported by American syphilologists. This book represents an excellent résumé of the most common complications of arsenic (arsphenamine) therapy and also of those complications arising from treatment with mercury and bismuth. Emphasis is placed on the value of tests of hepatic function. The book is to be recommended to those interested in this field of medicine.

The Thyroid and Its Diseases. By J. H. Means, M.D., Professor of Clinical Medicine, Harvard University. Price, $6. Pp. 602, with 73 illustrations. Philadelphia: J. B. Lippincott Company, 1937.

This book has a vivid personality. It owes its origin to the Massachusetts General Hospital, and no reader can forget this fact while progressing from the title page, with its reproduction of an old print of the Bulfinch Building, to the end of the volume.

The opening words of the preface introduce one to the point of view that is maintained throughout the volume: "While the present work is intended to be, in a measure, a textbook of the diseases, or disorders, of the thyroid, it is in no sense an encyclopedic treatise on that subject. Rather it is an account of the personal experience of a considerable group of workers in a single thyroid clinic and of the opinions and convictions derived from this experience. The clinic is that of the Massachusetts General Hospital and the period of observation now extends over more than two decades."

Thus, one is given the opportunity to read, so to speak, the log of a cruise in thyroidology, assembled by a group of explorers during a voyage which has lasted for approximately twenty years. That the traditions of canny New England seafaring ancestors still influence the Massachusetts General Hospital Thyroid Clinic is easily perceptible; for during this voyage all available charts, in the forms of literature concerning the thyroid gland, have been consulted, and when the "M. G. H. crew" have made soundings which have differed from those reported by other "thyroid mapmakers," these have been reported for readers to use or not, as they see fit.

The charm of the book lies in the manner in which it is written. It is more of a narrative than an ordinary textbook and therefore is unusually readable. One follows this group of adventurers up and down the shores and rivers of the thyroid gland, and thus one is taught thyroid geography; one learns of the habits and peculiarities of folk who happen to be afflicted with thyroid disease; one hears yarns such as one sailorman might tell another about thyroid history and the rumors of thyroid territory still undiscovered, with the riches said to be hidden there; and, to make the story complete, a great "Thyroid Storm" is described and how clever navigators may carefully pilot their patients through it to the shores of safety.

The book is well printed and is of convenient size. Beyond doubt the thyroid gland and its diseases are comprehensively discussed from a variety of points of view. The literature is well assembled, and the index is carefully constructed. Already one looks forward to the pleasure of reading the extensive revision of this book which the author hopes will be made in the future.

Die Vitamine und ihre klinische Anwendung. By W. Stepp, M.D., J. Kühnau, M.D., and H. Schroeder, M.D. Second edition. Pp. 189. Stuttgart: Ferdinand Enke, 1937.

This is the second edition of an excellent short book on the perplexing subject of the vitamins. Of the first edition, which appeared early in 1936, *The Journal of the American Medical Association* (**107:**1158 [Oct. 3] 1936) said, "This monograph affords an extraordinary amount of information in brief compass." This sentence well characterizes the second edition.

Part of the charm of the monograph lies in its simplicity; complicated terms or descriptions are not used, and any one with the least interest in the subject can easily follow the authors' ideas. The historical account of how general knowledge regarding the vitamins has grown is excellent; so is the chapter comparing vitamins and hormones. The body of the book, however, runs through the vitamin alphabet, beginning with a historical account of the discovery of vitamin A, going on with something regarding its chemistry, something regarding the experimental proof of its physiologic existence and a good deal regarding its clinical importance and

finally ending with a list of vitamin A preparations, with their dosage, now available for clinical use. All the other known vitamins are discussed, explained or even theorized over in similar fashion. Thus in a short book is assembled a large amount of material not only of great theoretic interest but also of considerable clinical importance.

While possibly at present some of the conclusions regarding the clinical value of certain of the vitamin preparations now on the market are not universally accepted, nevertheless the authors have been fair minded. They have put together a useful monograph that is well worth studying and that contains many stimulating ideas. It is no wonder that the first edition was promptly gobbled up, making necessary a second edition within a few months. How rapidly knowledge regarding the vitamins accumulates is well shown by the fact that, in order to be up to date and sufficiently comprehensive, the second edition is perforce fifty-nine pages longer than the first edition.

Röntgenologische und pathologisch-anatomische Studien über den tuberkulösen Primärkomplex. Acta radiologica, supplement 33. By J. Frimann-Dahl and Georg Waaler. Price, 9 kronor. Pp. 60, with 23 illustrations. Oslo: Nationaltrykkeriet, 1936.

This work represents a 56 page original contribution to phthisiology. Studies were made of 200 dissections, together with roentgenograms taken during life and after extirpation of the lungs. The material is analyzed for the frequency of occurrence of the primary complex, discrepancies between the clinical Pirquet test and the finding of the primary complex, the localization of the primary complex, the differential diagnosis of primary and additional infection, the visibility of the primary complex in the roentgenogram and other related problems.

The study represents a thorough investigation and supplies direct evidence regarding many controversial topics, for example, the appearance of nontuberculous calcification in the pulmonary fields in the roentgenogram and the differentiation of primary infection and reinfection.

Sero-Diagnostic Studies of Malignant Tumors: Experiments in Complement Fixation by Means of Lipoid Extracts. By Alfred Zacho. Pp. 185. Copenhagen: Levin & Munksgaard, 1936.

This is an exhaustive study of the complement fixation test for tumors. It is divided into ten chapters, each dealing with some phase of the reaction and its importance to the reaction. For one interested in working with the complement fixation test for diagnostic purposes, this monograph contains a great deal of valuable information.

The largest number of positive reactions to the complement fixation test for any one series of patients with carcinoma was only 34.2 per cent, and for some series as many as 24 per cent of the control noncancerous patients showed a positive reaction of the serum. The reactive power resides in the acetone-soluble fraction of fatty acids and particularly the cholesterol fraction. One must conclude, however, that for clinical purposes the reaction is, as yet, valueless.

Undersøgelser over en gruppe actinomyceter isolerede fra menneskets svaelg. By Rigmor von Magnus. With an English summary. Paper, 6 kroner. Pp. 132. Copenhagen: Levin & Munksgaard, 1936.

This monograph deals with observations on one hundred and thirty strains of branching bacteria found in the pharynx and nasopharynx of human beings. The morphologic, biologic and serologic characteristics and pathogenicity for animals were studied. The organisms occurred in about 41 per cent of the throats examined, although they appeared to play no etiologic role in any particular disease.